South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde

Vol. 24, No. 43 Cape Town, 28 October 1950 Weekly 2s

THE POLYSACCHARIDE LYSIS TEST

A NEW QUANTITATIVE TEST FOR *SALMONELLA TYPHI* ANTIBODIES

PRELIMINARY COMMUNICATION

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The high incidence of typhoid fever in this country presents a considerable problem to the laboratory which is required to provide as rapid a diagnosis as possible. For this purpose the Widal test is widely used, but it suffers from many drawbacks. Apart from the common failure of many proved cases to develop specific H-agglutinins (Felix and Olitzki, 1928-29) and the frequent anamnestic responses in T.A.B. immunized persons as well as their equally frequent failure to develop O-agglutinins (Wilson, 1945), agglutination of the normal test organism, *Salm. typhi* 901-0, is considerably affected by prozone phenomena (Hayes, 1947a) and by somatic phase variation (Kauffmann, 1941; Hayes, 1947b). The significance of the quantitative phase variation of the XII_3 component of the somatic antigen cannot be too highly stressed. When it is present and dominant, as in 901-0, it is highly agglutinable and antigenic. When it is recessive, as is the case in most human infections, it is of low antigenicity, produces a poor antibody response and releases the XII_1-XII_3 factors which become dominant.

We have found, in bacteriologically proved cases of typhoid fever, that almost always the O-titre for the homologous infecting organism is from 8 to 32 times greater than for the 901-0 strain, the local strains being XII_3 deficient.

A further line of investigation was suggested by the work of the Melbourne school (Burnet and Anderson, 1946; Keogh, North and Warburton, 1948) and of Middlebrook and Dubos (1948) who showed that specific bacterial polysaccharides can be adsorbed on to the surface of red blood cells and that these sensitized cells can then be agglutinated by sera containing specific bacterial agglutinins. A wide range of such complexes has been isolated and tested in the laboratory in this way. Middlebrook and Dubos applied the technique to the diagnosis of tuberculosis. They encountered certain irregularities in their agglutination tests which Fisher and Keogh (1950) showed could be overcome by the addition of complement. They demonstrated that when the sensitized cells were brought into contact with the specific antibody, the further addition of complement resulted in haemolysis. We have confirmed this observation in relation to *Salm. typhi* and developed a quantitative test for the corresponding antibodies using a somatic polysaccharide isolated from a local strain (T5) as the red cell sensitizing agent.

Acetone-dried bacterial bodies of *Salm. typhi* (T5) were prepared in bulk according to the method of Freeman, Challinor and Wilson (1940). On occasion six days' incubation in 75% acetone was required to kill all the organisms. Polysaccharide was extracted with ice-cold trichloracetic acid from 10 g. amounts (Boivin *et al.*, 1933), the final yield being of the order of 0.5% by weight. Washed, packed sheep cells preserved in 5% sodium citrate solution (Evans, 1950) were sensitized with 20 volumes of a 0.1% solution of the polysaccharide in normal saline for two hours at 37° C and resuspended, after three saline washes, to give a final 0.5% suspension. Experiments suggest that the ratio of cells to polysaccharide solution might be increased as a considerable amount of the latter remains in the final supernatant.

Sera from 50 cases of bacteriologically proved typhoid fever were inactivated and absorbed with unsensitized, packed sheep cells to remove heterophile antibodies (this could be obviated by using heterophile antibody-deficient cells such as rabbit cells). Doubling serum dilutions were made in 0.5 ml. volumes from 1:10 to 1:10,240 and to each was added an equal volume of sensitized cells and of complement diluted to contain one haemolytic unit (Kolmer). Appropriate controls were set up for each series of tests. After incubation for one hour at 37° C the tubes were read for haemolysis, the end point being taken as the highest serum dilution showing sparkling haemolysis.

Previous techniques have allowed antibody adsorption to continue for two hours at 37° C followed by 12-18 hours at 4° C before the addition of complement. On *a priori* grounds it appeared to us that the polysaccharide-antibody union should be instantaneous and that this long adsorption period should be unnecessary. Our results confirm this, parallel tests with the long adsorption period giving results identical with the short technique described above.

TABLE I: COMPARISON OF O-AGGLUTINATION AND POLYSACCHARIDE LYSIS TITRES

(Bacteriologically proved cases of typhoid)

Serum	*Agglutination titre*		*Polysaccharide Lysis Titre*
	901–0	*Homologous Strain*	
3399 T5*	200	3,200	2,560
2688 T21*	200	6,400	2,560
2361 T17*	200	3,200	640
713 T6*	200	3,200	1,280
5591 T1*	200	3,200+	10,240
4888 T4*	200	50	40
3400 T26*	100	800	2,560
500 T37*	100	800	2,560
3668 T37*	200	1,600	1,280
14627	20	20 (v. T5)	1,280
14630	80	160 (v. T5)	1,280
14635	10	40 (v. T5)	1,280
14712	160	640 (v. T5)	640
14636 Normal control	—	—	—
T-901-0 (Rabbit)	5,120	5,120	10,240
Vi (Rabbit)	—	—	—
Vi (Horse)	—	—	—

* Agglutination titres were determined on fresh serum, but the sera were stored frozen for 4–5 months before the polysaccharide lysis test.

A typical protocol is shown in Table I in which the agglutination titres to 901-0, T5 or the homologous *Salm. typhi* strains (O suspensions *boiled* for not less than six hours—see Hayes, 1947a) are compared with the polysaccharide lysis titre. Agglutination tests were all made by Felix' technique using 1 ml. serum dilution volumes and 1 drop of bacterial suspension standardized to an opacity equal to $6{,}000 \times 10^6$ *Esch. coli*, the titre being taken as the highest dilution not showing a discrete spot of unagglutinated bacteria after 2 hours' incubation at 37° C and standing on the bench overnight.

It will be seen that with one exception (4888T4), the polysaccharide lysis test (P.L.T.) appears to be as sensitive an indicator of somatic antibodies as the O-agglutination test, if not more sensitive. The P.L.T. is a more rapidly performed test taking only one hour after the reagents have been prepared and is much easier to read than O-agglutination. In the discrepant case, the organism was isolated from the faeces 20 days before the serum sample was taken, this being nearly seven weeks after the onset of the disease when one may reasonably expect a natural fall of both agglutination and P.L.T. titres (*vide infra*). However, the implications of this single observation are at present obscure, and the antigenic structure of the organism itself is being investigated further. The protocol also illustrates the considerable difference between the 901-0 and the homologous agglutination titres which we attribute to the 'XII-ishness' of the somatic antigens of the infecting strains.

TABLE II: SERIAL O-AGGLUTINATION AND POLYSACCHARIDE LYSIS TITRES

(Case 14832—inoculated 1 year previously)

Date	*O-Agglutination Titre*		*P.L.T.*	*Remarks*
	901–0	*T5*		
20 May	—	(not done)	160	Blood culture + H-titre negative.
23 May	80	160	640	H-titre negative. Treated with chloramphenicol.
28 May	160	320	1,280	
1 June	40	80	80	
13 June				Clinical relapse.
15 June	80	320	640	Blood culture + H-titre 200.

A further protocol of interest (Table II) shows the respective titres of an inoculated Indian who probably contracted a laboratory infection and whose blood culture was positive on the fourth day (20 May). The absence of antibodies in an inoculated person, the failure of the Widal test as a diagnostic aid and the contrasting usefulness of the P.L.T. even in the early stages of the disease are here self-evident.

Our purpose in publishing this preliminary note is to draw the attention of other workers in this field to what may prove to be a useful additional test in diagnostic bacteriology. At present we are attempting to simplify the preparation of the test reagents and to relate the test to other salmonellae containing the somatic antigens of *Salm. typhi*. The principle of the test is applicable to a wide variety of other infections, some of which we are investigating in parallel with this work (early experiments suggest it may be used in place of the gonococcal complement fixation test), and its extension may provide a valuable additional tool in the diagnostic laboratory's armamentarium.

ADDENDUM

Since this note was submitted for publication in June 1950, Adler (Proc. Soc. Exper. Biol. Med., 1950, **74,** 561) has also reported a specific haemolysis of this type with *S. typhi* 0-901 polysaccharide and rabbit immune serum, using sheep, rabbit and human erythrocytes.

REFERENCES

Boivin, A., Mesrobeanu, L. and Mesrobeanu, I. (1933): Compt. Rend. Soc. Biol., **114,** 307.

Burnet, F. M. and Anderson, S. G. (1946): Brit. J. Exper. Path., **27,** 236.

Evans, A. S. (1950): J. Lab. Clin. Med., **35,** 300.

Felix, A. and Olitzki, L. (1928-29): J. Hyg., **28,** 55.

Fisher, S. and Keogh, E. V. (1950): Nature, **165,** 248.

Freeman, G. G., Challinor, S. W. and Wilson, J. (1940): Biochem. J., **34,** 312.

Hayes, W. (1947a): Brit. J. Exper. Path., **28,** 98.

Idem. (1947b): J. Hyg., **45,** 14.

Kauffman, F. (1941): J. Bact., **41,** 127.

Keogh, E. V., North, E. A. and Warburton, M. F. (1948): Nature, **161,** 687.

Middlebrook, G. and Dubos, R. J. (1948): J. Exper. Med., **88,** 521.

Wilson, J. F. (1945): J. Hyg., **44,** 129.

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EDITORIAL

CARDIAC GLYCOSIDES

We publish in this issue of the *Journal* the results of some local investigations on a new glycoside named rubellin, obtained from *Urginea rubella* Baker. These observations suggest that this glycoside acts directly on the myocardium. Further clinical studies on this substance are to be made. The results will be of great interest because recently certain workers overseas have contradicted the orthodox pharmacological teaching on the digitalis glycosides.

The administration of a cardiac glycoside in pure form or as powdered digitalis in the treatment of congestive cardiac failure has become a matter of routine; yet there is still controversy about the site and mode of action of these drugs on the cardiovascular system, especially in man, and about the differences among the individual drugs in these actions. They have been called cardiac glycosides because they have been regarded as acting on the heart itself.

The beneficial effects of digitalis glycosides on the function of the myocardium in failure has been proved thoroughly by experiments on isolated hearts and on isolated strips of heart muscle. More recently certain observations have suggested that the main action of digitalis is not on the heart but elsewhere in the body. McMichael and Sharper-Schafer [1] confirmed the observation that digoxin decreases both the venous pressure and the cardiac output in normal men, and found that it raises output at the same time as it lowered venous pressure in some cases of heart disease. These workers measured central (auricular) pressures. It was concluded that digoxin given intravenously acts in heart failure by diminishing venous pressure. With g-strophanthin or ouabain McMichael [2] observed a direct stimulating action on the human heart in certain cases of failure.

Dock [3] felt that the findings of McMichael with digoxin might be true of patients in advanced low-output failure, in whom a rise in venous pressure causes a further decrease in cardiac output. It could not be true in ambulatory patients whose cardiac output rises with exercise or recumbency; in such cases the improvement produced by digitalis can only be due to its action on the heart. Dock also pointed out that the

1. McMichael, J. and Sharpey-Schafer, E. P. (1944): Quart. J. Med., **13**, 123.
2. McMichael, J. (1948): Brit. Med. J., **2**, 927.
3. Dock, W. (1946-1947): J. Mt. Sinai Hosp., **13**, 310.

VAN DIE REDAKSIE

HARTGLUKOSIEDES

In hierdie uitgawe van die *Tydskrif* publiseer ons die uitslae van 'n paar plaaslike ondersoeke in verband met 'n nuwe glukosied genaamd rubellien wat verkry is van *Urginea rubella* Baker. Hierdie waarnemings laat vermoed dat dié glukosied regstreeks op die hartspier inwerk. Verdere kliniese ondersoeke in verband met hierdie stof gaan uitgevoer word. Die uitslae sal van groot belang wees omdat sekere navorsers in die buiteland onlangs die ortodokse farmakologiese leer oor die digitalisglukosiedes weerspreek het.

Die toediening van 'n hartglukosied in suiwer vorm of as digitalis in poeiervorm het 'n roetinesaak geword by die behandeling van hartverswakking weens stuwing; nogtans is daar steeds meningsverskil oor die plek en wyse waarop hierdie geneesmiddels op die vaatstelsel van die hart, veral by die mens, inwerk en oor die verskille van die afsonderlike geneesmiddels by hierdie inwerkinge. Hulle is hartglukosiedes genoem omdat daar gemeen is dat hulle op die hart self inwerk.

Die heilsame gevolge van digitalisglukosied op die funksionering van die hartspier by verswakking is deeglik bewys deur eksperimente op geïsoleerde harte en op geïsoleerde repies hartspier. Kort gelede het sekere waarnemings daarop gedui dat die hoofwerking van digitalis nie op die hart is nie maar op 'n plek elders in die liggaam. McMichael en Sharpey-Schafer [1] het die waarneming bevestig dat digoksien by die normale mens beide die aardruk en die hartproduksie verminder en het gevind dat dit in sommige gevalle van hartkwaal die hartproduksie verhoog en terselfdertyd die aardruk verminder. Hierdie ondersoekers het sentrale (voorkamer-) druk gemeet. Daar is afgelei dat digoksien wat binne-aars toegedien word in die geval van hartverswakking inwerk deur die aardruk te verminder. Met g-strofantien of ouabain het McMichael [2] 'n regstreekse stimulering van die menslike hart waargeneem by sekere gevalle van verswakking.

Dock [3] het gemeen dat die bevindings van McMichael in verband met digoksien van toepassing mag wees op pasiënte wat aan gevorderde verswakking met lae hartproduksie ly, by wie 'n verhoging van die aardruk 'n verdere daling van die hartproduksie veroorsaak. Dit kon nie geld van pasiënte wat nie bedlêend is nie en van wie die hartproduksie toeneem wanneer hulle oefening neem of gaan lê; in sulke gevalle kan die verbetering deur digitalis te weeg gebring slegs te danke wees aan die inwerking daarvan op die hart. Dock het ook daarop gewys dat die kateter-tegniek slegs voorsiening maak vir waarnemings in verband met die

1. McMichael, J. en Sharpey-Schafer, E. P. (1944): *Quart. J. Med.*, **13**, 123.
2. McMichael, J. (1948): *Brit. Med. J.*, **2**, 927.
3. Dock. W. (1946-1947): *J. Mt. Sinai Hosp.*, **13**, 310.

catheter technique only allows observations of the immediate effect of intravenous digitalis preparations, and that gradual recovery of the heart muscle which the drug produces only becomes apparent after many hours.

Bloomfield *et al.*,[4] using newer techniques, found that ouabain acts directly on the failing heart by increasing its stroke output, this action preceding cardiac slowing or any decrease in peripheral venous or right ventricular filling pressure.

Wood and Paulett[5] investigated the action of digoxin by methods similar to those used by McMichael in patients with congestive cardiac failure with normal rhythm, and in others with raised venous pressure due to anaemia, thyrotoxicosis, acute nephritis, artificial hydraemia and chronic constrictive pericarditis. In the first group the injection of 1.5 mg. digoxin caused a fall in right auricular pressure and increase in output, but in the second group of patients who had no cardiac failure the injection had no effect on right auricular pressure. They concluded that this dose of digoxin given intravenously does not primarily lower the venous pressure, and suggested that in congestive heart failure its effect on venous pressure depends on its direct action on the heart. Wood[6] subsequently again denied that digitalis acts by lowering venous pressure, since he showed this action to be absent in patients with raised venous pressure and high cardiac output, but without heart failure.

In a recent study Walker, Lourie and Burn[7] compared the effects of ouabain and digoxin in the heart-lung preparation of the dog. They observed in the failing heart-lung preparation that both glycosides stimulate the heart and increase the cardiac output in the same way. They suggest that had McMichael used a much larger dose of digoxin as a single dose (4 mg.) he might have observed an effect on cardiac output and work as he did with the dose of ouabain used (1 mg.). They also consider whether in certain patients with heart failure in lung disease the method of estimating cardiac output was reliable.

The present status of the controversy may be summarized in the statement of two groups of workers:—

1. Wood and Paulett,[5] who suggest that the effect of digoxin on the venous pressure in congestive heart failure 'may yet depend upon its direct action on the heart, as originally believed;'

2. Walker, Lourie and Burn[7] who state that it appears 'reasonable to suppose that digoxin acts in heart failure as the digitalis glycosides have long been considered to act, namely, as direct stimulants of heart muscle'.

4. Bloomfield, R. A. *et al.* (1948): J. Clin. Invest., **27,** 588.
5. Wood, P. and Paulett, J. (1949): Brit. Med. J., **2,** 83.
6. Wood, P. (1950): Lancet, **2,** 181.
7. Walker, J. M., Lourie, E. M. and Burn, J. H. (1950): Brit. J. Pharmacol., **5,** 306.

onmiddellike uitwerking van die binne-aarse digitalispreparate en dat die geleidelike herstel van die hartspier wat die geneesmiddel teweegbring slegs na 'n hele paar uur merkbaar word.

Bloomfield *et al.*[4] het met gebruik van nuwe tegnieke gevind dat ouabain regstreeks op die verswakkende hart inwerk deur sy klopvermoë te verhoog en hierdie inwerking gaan die vertraging van die hart of 'n vermindering van die perifere aardruk of druk van die regtervoorkamer vooraf.

Wood en Paulett[5] het die werking van digoksien ondersoek met metodes soortgelyk aan dié wat deur McMichael gebruik is by pasiënte met hartverswakking weens stuwing en met normale ritme en by ander met verhoogde aardruk weens bloedarmoede, skildkliervergiftiging, akute nierontsteking, kunsmatige hidremie en kroniese ontsteking van die vernoude hartsak. By die eerste groep het die inspuiting van 1.5 mg. digoksien 'n daling in die druk van die regtervoorkamer en 'n styging in die hartproduksie veroorsaak, maar by die tweede groep pasiënte by wie daar geen hartverswakking was nie, het die inspuiting geen uitwerking op die druk van die regtervoorkamer gehad nie. Hulle het afgelei dat hierdie dosis digoksien wat binne-aars toegedien word, nie in die eerste plek die aardruk verminder nie en het gemeen dat by hartverswakking weens stuwing die uitwerking daarvan op die aardruk afhang van sy regstreekse werking op die hart. Wood[6] het daarna weer ontken dat digitalis deur verlaging van die aardruk inwerk aangesien hy bewys het dat hierdie werking nie voorkom nie by pasiënte met verhoogde aardruk en hoë hartproduksie maar sonder hartverswakking.

In 'n onlangse ondersoek het Walker, Lourie en Burn[7] die uitwerkinge van ouabain en digoksien in die hart-longpreparaat van die hond vergelyk. Hulle het gemerk dat by die verswakkende hart-longpreparaat beide glukosiede die hart stimuleer en op dieselfde wyse die hartproduksie verhoog. Hulle meen dat indien McMichael 'n baie groter dosis digoksien as enkele dosis (4 mg.) gebruik het, hy moontlik 'n uitwerking op die hartproduksie en werk van die hart sou waargeneem het soos met die dosis ouabain (1 mg.) die geval was. Hulle oorweeg ook of die metode om die hartproduksie te bereken vertroubaar was in die geval van sekere pasiënte met hartverswakking by longkwaal.

Die huidige stand van die geskil kan opgesom word in die verklaring van die twee groepe navorsers:—

1. Wood en Paulett,[5] wat te kenne gee dat die uitwerking van digoksien op die aardruk by hartverswakking weens stuwing ‚nog steeds kan afhang van sy regstreekse inwerking op die hart, soos oorspronklik gemeen is;'

2. Walker, Lourie en Burn[7] wat verklaar dat dit lyk of dit ‚redelik is om te veronderstel dat digoksien by hartverswakking inwerk soos daar reeds lank gemeen is dat die digitalisglukosied inwerk, naamlik as 'n regstreekse stimuleringsmiddel van die hartspier.'

4. Bloomfield, R. A. *et al.* (1948): *J. Clin. Invest.*, **27,** 588.
5. Wood, P. and Paulett, J. (1949): *Brit. Med. J.*, **2,** 83.
6. Wood, P. (1950): *Lancet*, **2,** 181.
7. Walker, J. M., Lourie, E. M. en Burn, J. H. (1950): *Brit. J. Pharmacol.*, **5,** 306.

RUBELLIN—A NEW DIGITALIS-LIKE DRUG FOR HEART DISEASE*

SOME EXPERIMENTAL AND CLINICAL EXPERIENCES WITH ITS USE

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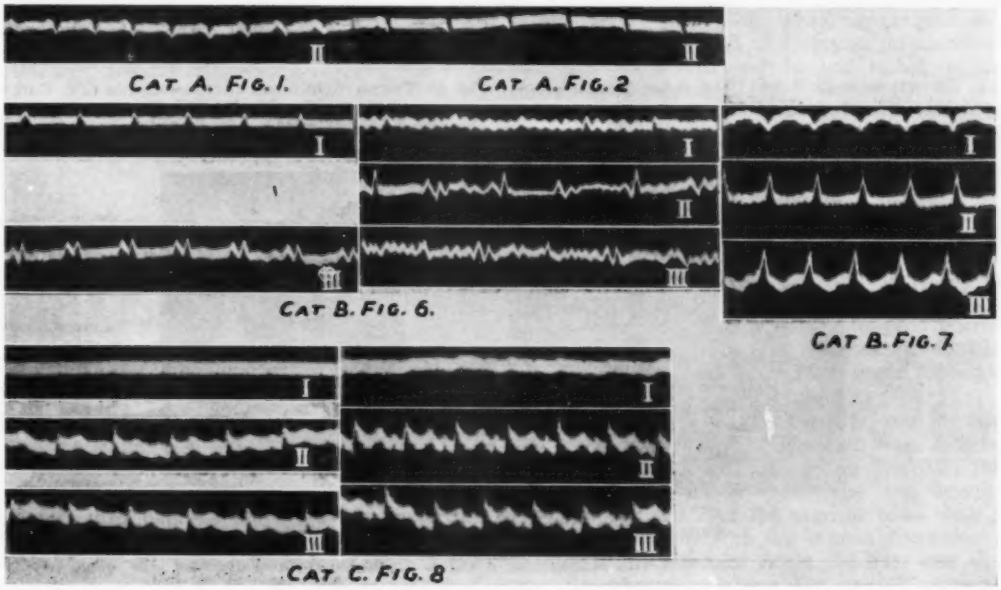
Rubellin is a glycoside which has been isolated from Urginea rubella by Louw of Onderstepoort, Transvaal. The genus Urginea, belonging to the natural order Liliaceae is closely related to the genus Scilla. Watt and Breyer-Brandwyk (1932) in 'Medicinal and Poisonous Plants of South Africa' have described Urginea burkei, Urginea altissima, Scilla rigidifolia, and the bulb of Scilla cooperi.

The pharmacological action of the compound has been investigated by Sapeika (1944), who found the glycoside to have a digitalis-like action. He determined the potency of Rubellin by carrying out assays on frogs, using Ouabain as a standard of comparison. He came to the conclusion that the potency of Rubellin, which is a highly soluble crystalline glycoside, compared with that of Ouabain as 1.20 to 1.

Experimental Work on Rubellin. The dose of Ouabain used by Smith (1942), Chavez (1943), Paul White (1944), on human beings, was 0.25 mg. The potency of Rubellin to Ouabain being 1.20 to 1, I therefore took 5/6th of 0.25 mg., i.e., 0.21 mg. as the dosage for the initial experiments. These were performed on cats, and, regarding 0.21 mg. as the dose for an average man of 70 kg. bodyweight, 0.003 mg. per kg. bodyweight was

* Abridgment of thesis submitted for the degree of Doctor of Medicine of the University of Edinburgh, for the publication of which kind permission has been granted by the Faculty of Medicine of that University.



CAT A. Dose 0.003 mg. Rubellin per kg. body weight.
Fig. 1. Before injection. Rate 250 beats per minute.
Fig. 2. Fifty minutes after second injection. Rate 158 beats per minute.

CAT B. *Experiment* 2. May 22. Dose 0.012 mg. Rubellin per kg. body weight.
Fig. 6(*a*). Before injection. Rate 167 beats per minute.
Fig. 6(*b*). Two hours after injection. Rate 140 beats per minute. Impure auricular flutter.

CAT B. *Experiment* 3. May 25. Dose 0.12 mg. Rubellin per kg. body weight.
Fig. 7. Forty-five minutes after injection. Rate 214 beats per minute. Ventricular paroxysmal tachycardia.

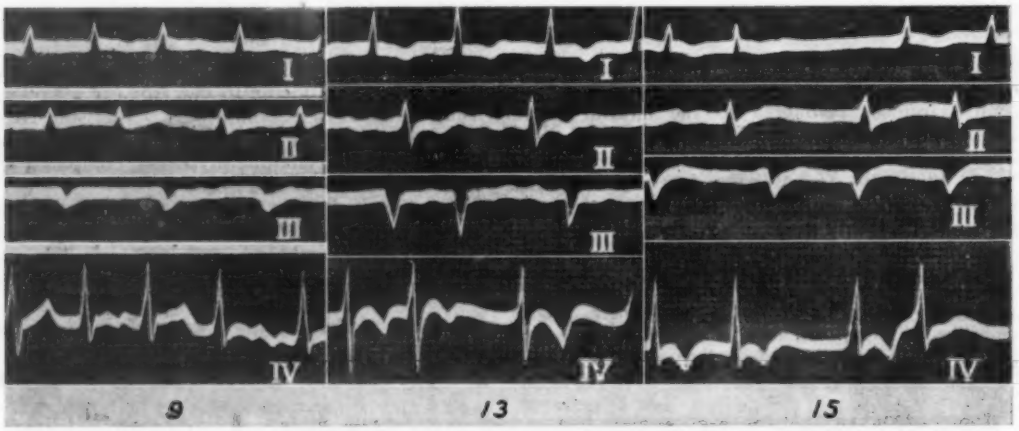
CAT C. Dose 0.012 mg. Rubellin per kg. body weight.
Fig. 8(*a*). Before injection. Rate 158-167 beats per minute.
Fig. 8(*b*). Fifty-five minutes after injection. Rate 188 beats per minute. Widening of QRS.

used as the initial dose for investigations on the cat. Starting with 0.003 mg. per kg. increasing doses were given, and the effects on the electrocardiograms were noted.

The cats were weighed before each experiment, and after being anaesthetised with ether, the femoral vein was exposed, and the Rubellin, dissolved in distilled water, was injected in the dosage indicated above.

When 0.003 mg. and 0.006 mg. Rubellin per kg. bodyweight was injected in cats, reduction in the heart rate with slight flattening of the RS-T wave in cardio, gram was observed. When 0.012 mg. was injected, impure auricular flutter with reduction in heart rate was produced. In another case the same dose produced paroxysmal ventricular tachycardia followed by death within 48 hours. The same dose produced in another cat widening of the QRS complex (intraventricular block). This cat died within six hours.

Estimation of the Dose of Rubellin on Human Beings. The experiments on the cats proved that while a dose of 0.012 mg. Rubellin per kg. produced toxic signs, it was safe to use the smaller dose of 0.006 mg. On proceeding to the experiments on human beings, it seemed reasonable to assume that the human heart would react in the same way as that of the cat. Yet it was necessary to proceed with caution. Rubellin was a new drug and had never been used clinically, and it was possible that human beings would not react in exactly the same way as animals. Pick (1940) says, 'frog units and cat units cannot nor ought to serve as a basis for therapeutic dosage, nor may they be used for comparing the therapeutic values of different glycosides. They give us only

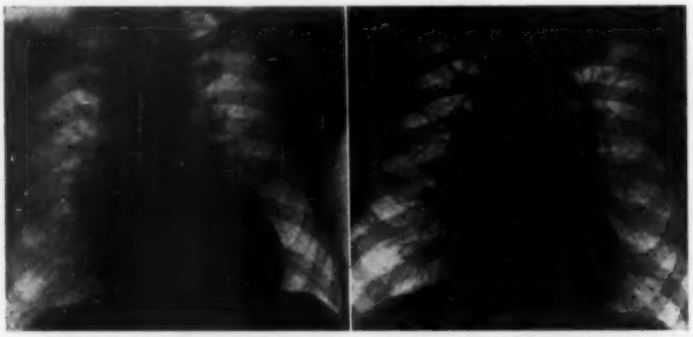


CASE 1 (C.J.). Dose 0.21 mg. Rubellin (four injections).

Fig. 9. Before treatment. Rate 135 beats per minute.

Fig. 13. One hour after third injection. Rate 105 beats per minute. Depressed S-T_1. Inversion T_1, T_2, T_3.

Fig. 15. Twenty-eight hours after fourth injection. Rate 105 beats per minute. Depressed S-T_1. Inversion T_1 and T_4. Diphasic T_2. Upright T_3.



Case 1 (C.J.)
Before treatment with Rubellin.
P.A. view. 27.8.1945.

Case 1 (C.J.)
After treatment with Rubellin.
P.A. view. 3.9.1945

those values which have been gained on the basis of lethal doses on frog and cat units'. Standard values as elaborated in animal experiments cannot be used indiscriminately for therapeutic purposes.

In view of this, I decided to use the initial dose of 0.003 mg. Rubellin per kg., repeating the dose according to the condition of the patient. In an average man of 70 kg. bodyweight, the dose was therefore 0.21 mg. This, dissolved in 2 cc. of distilled water, was prepared for me in ampoules. To this was added sterile distilled water, or sterile saline, up to 10 cc. and the injection was given intravenously.

Selection of Patients for Study. The patients showing some or all of the following evidences of congestive heart failure while in hospital, were selected for experiment.

1. Congestion of the lungs.
2. Enlarged liver.
3. Ascites or peripheral oedema.
4. Dyspnoea.
5. Orthopnoea.
6. Dilatation of the veins of the neck.

Patients with auricular flutter and those with signs of left ventricular failure were included in this study.

If, during the period of observation, the ventricular rate declined to normal levels, and at the same time the signs and symptoms of failure subsided as a result of bed rest alone, such patients were excluded from this study. Those patients who had received digitalis within the previous fortnight were also excluded. In the majority of the cases chosen, the preliminary period of observation was omitted because immediate intravenous therapy with Rubellin was necessary, the condition being critical. When the condition of the patient permitted, a roentgenogram was taken at six feet before and after treatment to determine the diminution of the size of the heart, if any. Most of the patients, however, could not undergo this as they were too ill to be moved. Where possible, patients were weighed before and after treatment as loss of weight was an indication of the patient's progress in congestive cardiac failure. The amount of fluid intake was limited.

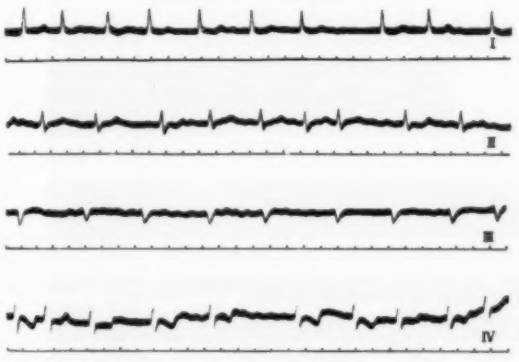


Fig. 21. Nineteen days after fourth injection. Rate 95 beats per minute. Upright T_1, T_2, T_3, T_4—some complexes inverted and some upright.

The progress of the patient was measured by electrocardiograms taken before treatment and at varying intervals between injections. The chest lead used was CR_4. Venous pressure and circulation-time (decholin method) readings were taken. This was not always possible on account of the extent of the oedema, or because of the poor type of veins.

Improvement was judged by:

1. General appearance of the patient.
2. Lessening of orthopnoea.
3. Decrease of dyspnoea.
4. Improvement in pulse volume.
5. Diminution of restlessness and general excitement as shown by drowsiness and the occurrence of sleep.
6. Disappearance of gallop rhythm and pulsus alternans.
7. Diminution of oedema as judged by weight loss.
8. Slowing of ventricular rate.
9. Diminution of venous pressure in congestive cardiac failure.
10. Improvement in circulation time.

The following are some of the cases dealt with.

CASE 1

C.J. male, 48, was admitted into the Groote Schuur Hospital on Aug. 27th, 1945 in congestive cardiac failure. He complained of dyspnoea on exertion for the past five years. Although he had rested in bed for a fortnight, his condition had become worse. The neck veins were distended. There was slight pitting oedema round the ankles. The liver was three fingerbreadths below the costal margin and there were moist sounds at the bases of both lungs. The apex beat was in the sixth intercostal space outside the nipple line and fibrillating. Blood pressure 190/110 mm. Hg, pulse rate between 130 and 140. X-ray of heart on 27th of August before treatment showed enlargement of hypertensive shape (Dr. J. N. Jacobson). 'Cardio-thoracic ratio of 6.7:12. Passive hyperaemia of lungs. Superior vena cava dilated. Atheroma of the aortic knuckle. The prominent pulmonic arc suggests some associated right ventricular change.'

As there was no improvement on rest for two weeks prior to admission, he was given on Aug. 28th and 29th, a total of four injections of Rubellin, 0.21 mg. each. On the evening of the 28th Aug. the dyspnoea had subsided. On the 29th the cervical veins were less distended and on the 30th the venous distension was not in evidence. By the 1st Sept., the liver had receded to one fingerbreadth below the costal margin. From Aug. 28th to Sept. 3rd the loss of weight was 6½ lb. and there was a diminution in cardiac rate from 135 to 82. Effect of Rubellin began to wear off 28 hours after the fourth injection when T_2 became diphasic and T_3 upright (Fig. 15). The electrocardiogram taken 19 days later showed no changes as compared with the tracing taken before treatment with the exception of lead 4 (Fig. 21). The earliest changes to occur in the electrocardiogram were depression of S-T_1 and S-T_4.

X-ray of heart after treatment with Rubellin Sept. 3rd 1945 (Dr. J. N. Jacobson). 'The heart has decreased markedly in size; cardio-thoracic ratio now 5.5:12. Pulmonic arc much less prominent. Shape of heart practically normal. The superior vena cava has now assumed practically normal proportions. Still marked passive congestion of lungs. In right oblique, no abnormality noted except general backward curvature of oesophagus due to generalised cardiac enlargement. In the left oblique, the left ventricle shows some enlargement.

'*Conclusion.* The appearances are those of a hypertensive heart which radiologically shows considerable improvement.'

CASE 2

J.G. male, 45, was admitted per stretcher into hospital on 14 September 1945. He had syphilitic aortitis with left ventricular hypertrophy and dilatation, pulmonary congestion and oedema and pulmonary infarcts. He complained of cough of five months' duration, dyspnoea two months, oedema of the feet, legs and thighs one month. He had paroxysmal nocturnal dyspnoea one month, tenderness in the right hypocondrium seven days, haemoptysis two days. The apex beat was difficult to palpate. Cardiac dullness was increased to the left to the anterior axillary line. There was no dullness in the second left intercostal space. No thrills were present. Systolic and diastolic murmurs were heard and were of maximum intensity over aortic area. Gallop rhythm to the right of apex beat. Blood pressure 130/60 mm. Hg. Heart rate 92. Venous pressure (14 September) 220 mm. of water.

At the outset the patient was in a very critical condition. Rubellin was therefore given immediately. From the 14th to the 16th September he received a total of five injections, each 0.21 mg.

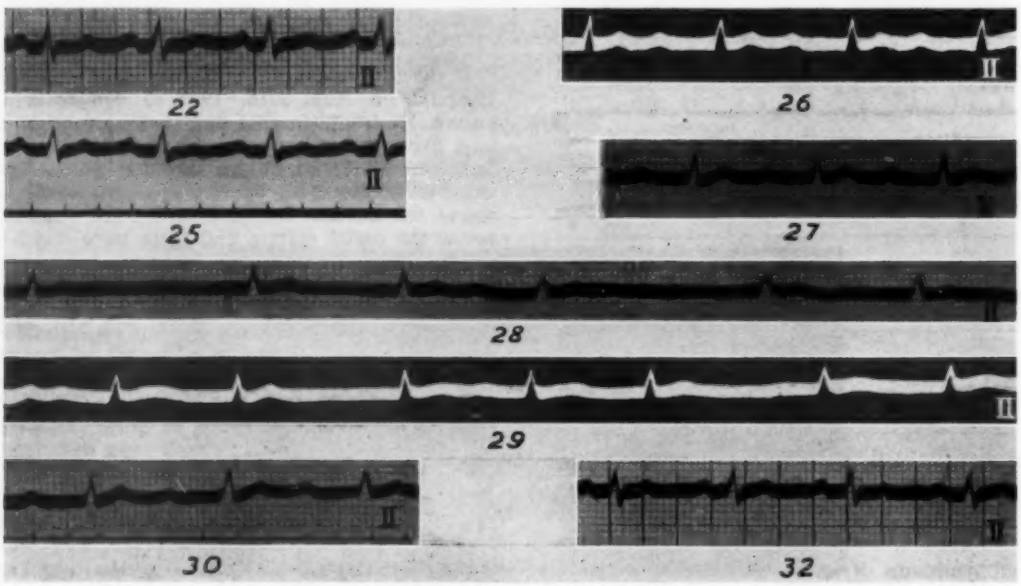
Changes noted were:

(*a*) Slowing of the heart rate with prolongation of P-R interval.

(*b*) Drop in venous pressure from 220 to 150 mm. of water. (September 14-19.)

(*c*) Loss of weight 1¼ lb. in five days.

The heart rate decreased from 94 to 79 beats per minute after the third injection, while the P-R interval was prolonged to 0.32 seconds (Fig. 26). Half an hour after the fifth injection the heart rate decreased to 65



CASE 2 (J.G.). Dose 0.21 mg. Rubellin (five injections).

Fig. 22. Before treatment. Rate 94 beats per minute. P−R = 0.16 seconds (Venous pressure 220 mm. water)

Fig. 25. One and three-quarter hours after second injection. Rate 94 beats per minute. P−R=0.20 seconds.

Fig. 26. Sixteen hours after third injection. Heart rate 79 beats per minute. P−R=0.32 seconds.

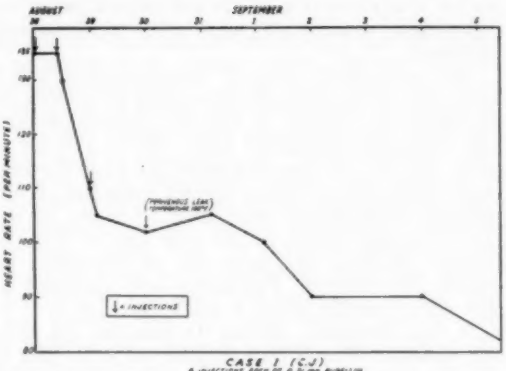
Fig. 27. One hour after fourth injection. Rate 79 beats per minute. P−R=0.32 seconds.

Fig. 28. Half-an-hour after fifth injection. Auricular fibrillation. Heart rate 65 beats per minute.

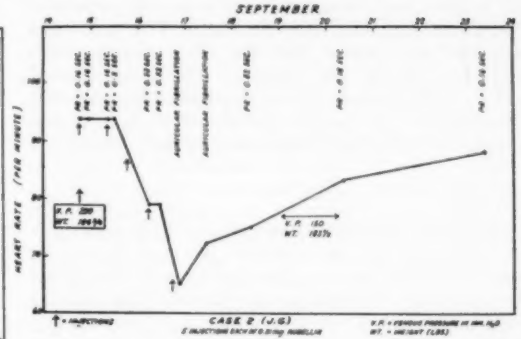
Fig. 29. Fourteen-and-a-half hours after fifth injection. Auricular fibrillation. Rate 72 beats per minute.

Fig. 30. Thirty-eight-and-a-half hours after the fifth injection. Regularity returning. Heart rate 75 beats per minute. P−R=0.32 seconds (Venous pressure 150 mm. water).

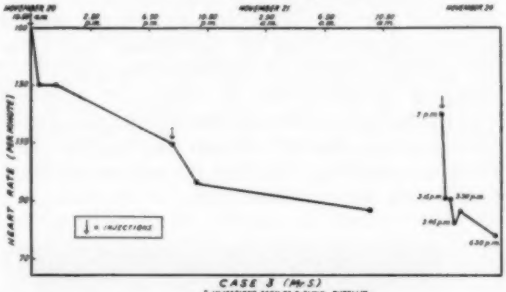
Fig. 32. Six-and-a-half days after the fifth injection. Heart rate 88 beats per minute. P−R=0.16 seconds.



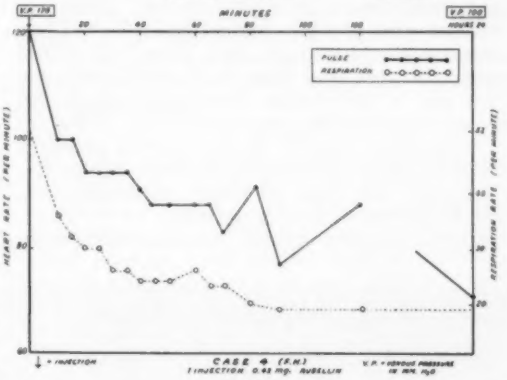
CASE 1 (C.J.)
6 INJECTIONS EACH OF 0·01 mg. RUBELLIN



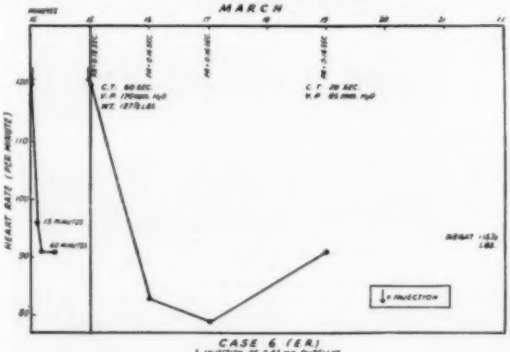
CASE 2 (J.G.)
5 INJECTIONS EACH OF 0·01mg. RUBELLIN



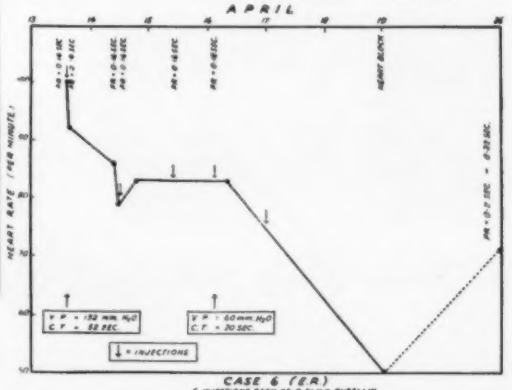
CASE 3 (Mr S.)
3 INJECTIONS EACH OF 0·01 mg. RUBELLIN



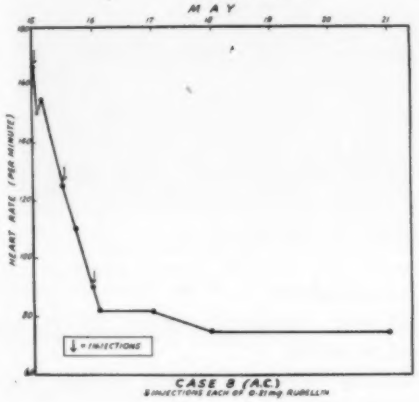
CASE 4 (F.M.)
1 INJECTION 0·02 mg. RUBELLIN



CASE 6 (E.R.)
1 INJECTION OF 0·02 mg. RUBELLIN
EXPERIMENT 1



CASE 6 (E.R.)
5 INJECTIONS EACH OF 0·01 mg. RUBELLIN
EXPERIMENT 3



CASE 8 (A.C.)
5 INJECTIONS EACH OF 0·01 mg. RUBELLIN

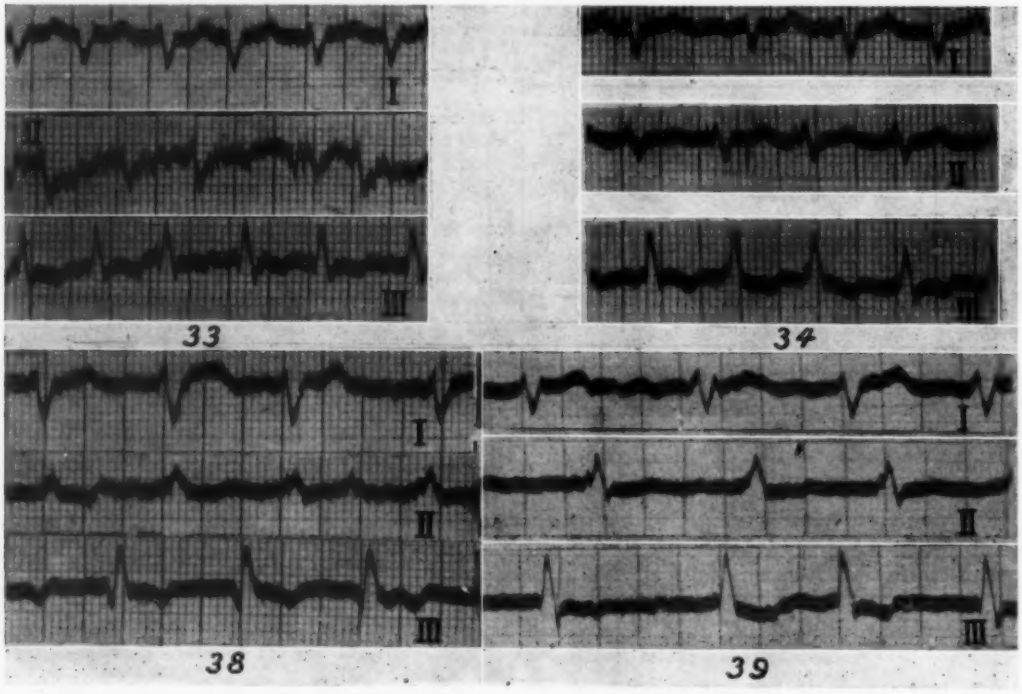
beats per minute and auricular fibrillation was produced (Fig. 28). Here Rubellin was withheld. The rate then increased and 38½ hours after the fifth injection was 75 beats per minute and regular. The P-R interval remained at 0.32 seconds. Six and a half days after the fifth injection, the rate was 88 and the P-R interval was 0.16 seconds, as at the commencement of the experiment.

CASE 3

Mr. S., male 70, was admitted into hospital 19 November 1945 in congestive cardiac failure. He complained of shortness of breath. On examination he was dyspnoeic and Cheynes-Stokes breathing was present. The cervical veins were distended. Liver was tender and extended to one fingerbreadth below the costal margin. There was sacral oedema and oedema round the ankles. Chest dull to percussion over the right base. There was cardiac enlargement, the apex beat being in the fifth intercostal space, five and a half inches from mid-sternal line. There was auricular fibrillation with heart rate of 148 per minute. Pulse 100, irregular. Radial arteries palpable, thickened and tortuous. Blood pressure 160/100 mm. Hg. Venous pressure 100 mm. of water, circulation time (decholin) 39 seconds on 20 November.

The electrocardiogram showed auricular fibrillation and a ventricular rate of 150 per minute, defective intraventricular conduction with QRS=0.12 seconds. S_1 widened.

He was given a total of three injections of 0.21 mg. Rubellin, the first on 20 November at 10.50 a.m. after a night's rest. Within 30 minutes following the injection the heart rate decreased from 150 to 130 per minute (Fig. 34). At 8.30 p.m. the same day when the heart rate had decreased to 110, a second injection of the same strength reduced the heart rate to 96 by 10 p.m. On 21 November, 9.50 a.m. the rate was 86 (Fig. 38). No further injection was given. On 24 November his condition deteriorated. The heart rate increased to 120. He was therefore given a third injection at 3 p.m. of 0.21 mg. Rubellin. Within 15 minutes the heart rate decreased to 90 and by 6.30 p.m. the heart rate was 77. Cheynes-Stokes breathing disappeared after the third injection. On 26 November the venous pressure was 61 mm. of water and the circulation time 27 seconds. No further injection of Rubellin was given in order to ascertain the persistence of effect. On 5 December at 11.15 p.m. he again became breathless, cold, and clammy. The heart rate was 140. He was then further treated with Ouabain and Dig. Fol. The persistence of effect therefore in this case was nine days.



CASE 3 (Mr. S.). Dose 0.21 mg. Rubellin (three injections).

Fig. 33. Before treatment. Heart rate 150 beats per minute. QRS 0.12 seconds.

Fig. 34. Thirty minutes after first injection. Rate 130 beats per minute.

Fig. 38. Thirteen and one-fifth hours after second injection. Rate 86 beats per minute.

Fig. 39. Forty-four hours after the third injection. Heart rate 80 beats per minute.

CASE 4

F.H., female 55, was admitted into hospital per stretcher on the morning of 14 January 1946. She complained of cough and haemoptysis, three days: dyspnoea even when resting, three weeks, and swelling of the feet and ankles. Her face was pale and anxious-looking. She was in distress with a respiration of 52 per minute. The cervical veins were distended. There was swelling of both feet with pitting oedema. The liver was four fingerbreadths below the costal margin and tender. Dullness in both lung bases with crepitations present. The apex beat was in the sixth intercostal space five inches from the mid-sternal line. The cardiac rate was 120 beats per minute (Fig. 45), and tic-tac rhythm was present. The second pulmonic sound was accentuated. The blood pressure was 190/110 mm. Hg. The venous pressure was 175 mm. of water. She was in congestive cardiac failure, hypertensive in origin.

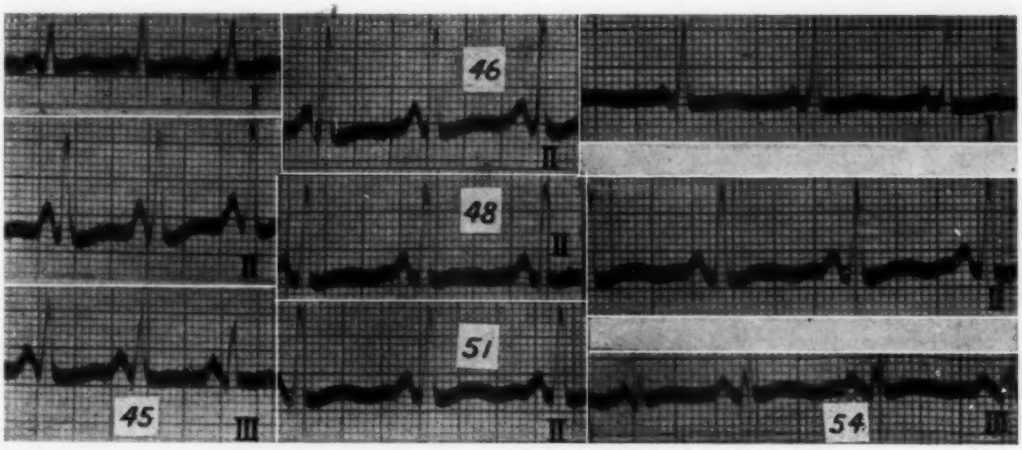
One injection of 0.42 mg. Rubellin (a double dose) was given about 12 hours after admission because her condition was desperate. The results were dramatic. No morphine was given. Within 10 minutes there was a diminution in the heart rate to 100 (Fig. 46), and in 20 minutes to 94. The respiratory rate decreased to 36 and 30 respectively. Within 30 minutes she was dozing with a respiration of 26. Within 65 minutes she was asleep with a heart rate of 88 and respiration of 23 (Fig. 51). Ninety minutes after the injection the heart rate was 77 and the respiratory rate 19. The blood pressure showed little change—180/110 mm. Hg. Twenty-four hours after the injection the heart rate was 71 (Fig. 55), the venous pressure was 100 mm. of water, and the circulation time 15 seconds.

Before the injection the P_2 wave in the cardiogram was 3.5 mm. in height and the R_2 12 mm. After injection the P_2 was 2 mm. in height when R_2 was still 12 mm. The tall and broad P_2 and P_3 waves are probably indicative of right auricular stress in a patient with severe congestive cardiac failure. These P waves became less broad and smaller after injection of Rubellin and seemed to indicate diminution of right auricular stress as the venous pressure, circulation time and congestive failure diminished. There were no toxic effects after the injection. The liver receded to two fingerbreadths below the costal margin. The oedema disappeared. The crepitations in the chest diminished and the cough improved. She felt easier. There was a loss of 7½ lb. in weight from 14 to 25 January. Digitalis was not given during the rest of her stay in hospital. Her condition remained the same till her discharge on the 31st.

It is possible that morphine would have produced the same results, but here the single dose of Rubellin gave the desired effect.

CASE 6

E.R., male 40, admitted into hospital 11 March 1946 complaining of cough, 10 years, 'asthma', three years, dyspnoea on exertion, three weeks, swelling of the feet, three weeks. The patient did not appear to be short of breath and he could lie flat without discomfort. The cervical veins were dilated, and there was oedema of the feet and legs extending up to the sacrum. There was no clubbing of the fingers and no cyanosis or pallor. The glands were not enlarged. The liver extended down to the umbilicus and was tender. The abdomen was distended and ascites was present. No crepitations were heard in the lungs. The pupils reacted to light and



CASE 4 (F.H.). Dose 0.42 Rubellin (one injection).

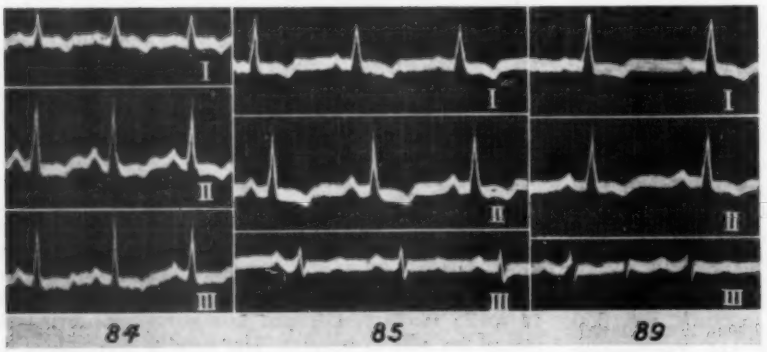
Fig. 45. Before injection. Rate 120 beats per minute. (Respirations 52 per minute). P_2 3.5 mm., R_2 12 mm.

Fig. 46. Ten minutes after injection. Rate 100 beats per minute (Respirations 36 per minute).

Fig. 48. Thirty minutes after injection. Rate 94 beats per minute (Respirations 26 per minute).

Fig. 51. Sixty-five minutes after injection. Rate 88 beats per minute (Respirations 23 per minute).

Fig. 54. One hundred and twenty minutes after injection. Rate 88 beats per minute (Respirations 19 per minute). P_2 2 mm., R_2 12 mm.

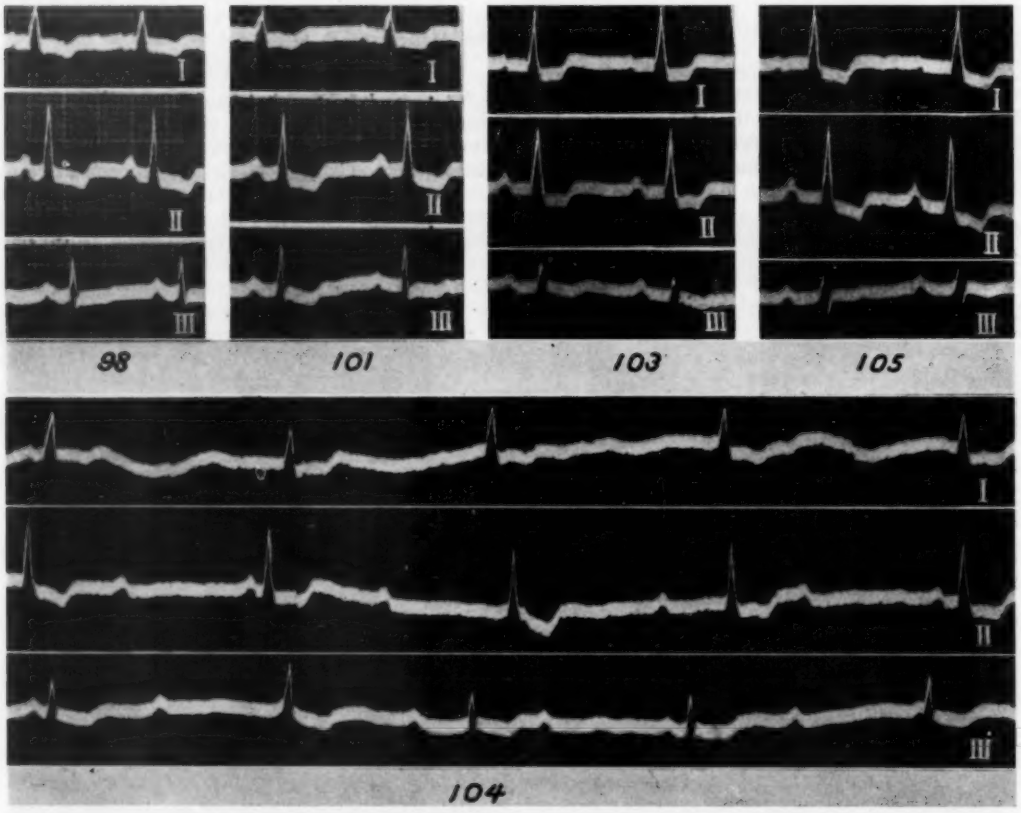


CASE 6 (E.R.) *Experiment* 1. Dose 0.42 mg. Rubellin (one injection).

Fig. 84. Before treatment. Rate 120 beats per minute. P−R=0.12 seconds.

Fig. 85. Twenty-five minutes after injection. Rate 91 beats per minute. P−R=0.14 seconds.

Fig. 89. Forty-four hours after injection. Rate 79 beats per minute. P−R=0.16 seconds.



CASE 6 (E.R.). *Experiment* 3. Dose 0.21 gms. Rubellin (five injections).

Fig. 98. Before first injection. Rate 100 beats per minute. P−R=0.14 seconds.

Fig. 101. Three-quarters of an hour after the second injection. Rate 79 beats per minute. P−R=0.16 seconds. S-T_1, S-T_2 and S-T_3 more depressed.

Fig. 103. Nine hours after the fourth injection. Rate 83 beats per minute. P−R=0.18 seconds. S-T_1 and S-T_2 still more depressed.

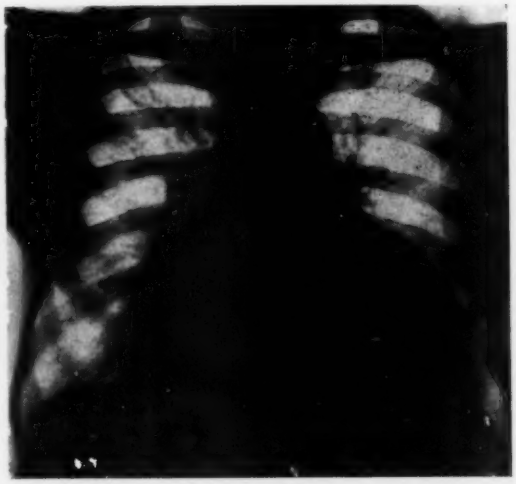
Fig. 104. Two days after the fifth injection. Rate 50 beats per minute (Heart block). S-T_1, S-T_2 and S-T_3 still more depressed.

Fig. 105. Nine days after the fifth injection. Rate 71-77 beats per minute. P−R=0.20/0.22 seconds.

accommodation. The retinal arteries showed some sclerosis. There was no nipping of veins. Haemorrhage and exudates were not present. Weight on 14 March was 127½ lbs.

The heart was enlarged, and the apex beat was in the sixth intercostal space, four inches from the mid-sternal line. There was dullness to the right of the sternum. The heart rate was 120 beats per minute. The heart sounds were faint. Gallop rhythm at the apex. Blood pressure 150/120 mm. mercury, venous pressure 170 mm. water, circulation time 60 seconds. The X-ray of the heart showed enlargement to the right and the left. The lung fields showed no signs of passive hyperaemia.

The etiology of this case was interesting in that, although both sides of the heart were enlarged, there were no congestive signs in the lungs, both on clinical and radiological examination. Parkinson (1936) stated,



Case 6 (E.R.)

Before treatment. P.A. view.

13 March 1946

'when considerable enlargement of the heart is encountered and no single cause or combination of causes seem sufficient to account for it, a past hypertension or a latent mitral stenosis may be responsible for it, for the characteristic murmur may sometimes be lacking over a long period. Similarly an unusual combination of congenital defects may account for such a difficult problem'.

In this case, the diastolic pressure was high throughout and the systolic rose during treatment as the following chart shows.

14 March	Blood pressure	..	150/120
16 March	,,	..	195/135
3 April	,,	..	165/125
16 April	,,	..	170/120
17 May	,,	..	180/120

From this it can be concluded that hypertension was one etiological factor. An unexplained congenital factor may be another reason. The absence of passive pulmonary hyperaemia may suggest a clinical diagnosis of Bernheim's syndrome (Russek and Zohman 1945); 'the diagnosis is suggested when a patient with left ventricular hypertrophy shows signs of right heart failure as the first indication of circulatory stress with venous distension of the neck and an enlarged liver. The mechanism is produced as the result of stenosis of the cavity of the right ventricle through displacement of the interventricular septum due to marked enlargement of the left ventricle resulting in obstruction to blood flow through the right ventricle. Dypsnoea and other signs of pulmonary congestion are absent until the end when left ventricular failure supervenes'. Paul White expresses doubt as to its entity. Fishberg (1940) says that he has observed many necropsies which support Bernheim's views. Russek and Zohman state that two other signs may occur, viz :

1. While the venous pressure is appreciably elevated the circulation time may remain within normal limits.
2. The electrocardiogram may show right axis deviation in a case of left ventricular hypertrophy.

These signs were not evident in this case.

The patient stated that he had received a good mixed diet while at work. He took no alcohol. As the symptoms and signs remained unchanged after four days in hospital on the usual hospital diet and thiamine chloride, beriberi was excluded and treatment with Rubellin for the cardiac failure was begun. This was divided into three experiments.

1. One injection of 0.42 mg. Rubellin, 15 March.
2. One injection of 0.5 mg. strophanthin-G, 28 March.
3. Five injections of 0.21 mg. Rubellin, 13 April.

Experiment 1. Within 44 hours after the injection, the heart rate decreased from 120 to 79 beats per minute, the P-R interval was prolonged from 0.12 seconds to 0.16 seconds (Fig. 89). The venous distension in the neck had disappeared and the liver was only two fingerbreadths below the costal margin.

Four days after the injection the heart rate was 91 beats per minute (Fig. 90), the circulation time decreased from 60.5 seconds to 28 seconds and the venous pressure from 170 mm. of water to 85. The total loss of weight in the experiment was 11½ lb. An X-ray taken on 18 March showed no reduction in the size of the heart although his condition had improved clinically. The effect of the Rubellin lasted seven days till 22 March, when the pulsation in the neck commenced again, the liver was three fingerbreadths below the costal margin, and the gallop rhythm returned.

Experiment 2. On 28 March 0.5 mg. strophanthin-G was injected for the purpose of comparison. Forty minutes after the injection the gallop rhythm disappeared and there was no pulsation in the neck.

The effect of the strophanthin lasted four days. Then the pulsation in the neck appeared again and the liver extended to four fingerbreadths below the costal margin.

Twenty grains dig. fol. were given in the period 1 April to 8 April. The heart rate decreased to 81 beats per minute and the P-R interval was prolonged to 0.16 seconds. There was no pulsation in the neck, and the liver was two fingerbreadths below the costal margin.

The effect lasted five days. On 13 April the gallop rhythm returned, the venous pulsation commenced again, the liver was four fingerbreadths below the costal margin, the venous pressure was 132 mm. of water, and the circulation time was 52 seconds.

Experiment 3. At this point 0.21 mg. Rubellin was given daily. Five injections were given altogether. The heart rate decreased after each injection, and after the fourth injection it was 83, the P-R interval being prolonged from 0.14 seconds to 0.18 seconds (Fig. 103). The circulation time was reduced from 52 to 28 seconds. The venous pressure was reduced from 132 to 60 mm. of water, and the liver was two fingerbreadths below the costal margin.

A fifth injection of 0.21 mg. Rubellin was then given to study further effects. The Wenckebach phenomenon ensued with a rate of 50 to the minute (Fig. 104).

During this last experiment each succeeding injection produced a deeper depression of the S-T segment, a prolongation of the P-R interval and a slower heart rate. The cumulative effect of Rubellin is thus demonstrated. The persistence of effect of 0.42 mg. of Rubellin was longer than that of 0.5 mg. strophanthin-G.

At the end of treatment an electrocardiogram taken on 26 April, nine days after the last injection of Rubellin, showed that the cardiac rate had increased from 50 to 71/77 beats per minute, the P-R interval was 0.2/0.22 seconds. The heart block had disappeared (Fig. 105).

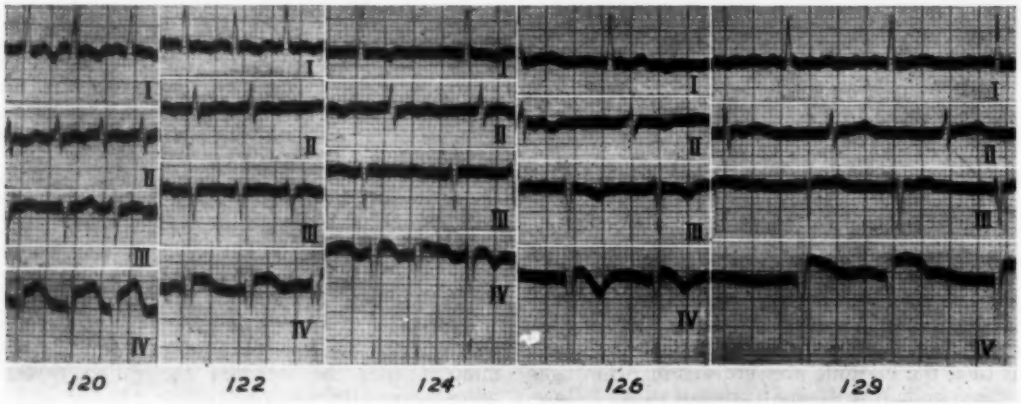
Dig. fol. was given by mouth again with better effect than on the first occasion. This was probably due to the reduced congestion in the alimentary tract leading to the better absorption of the drug.

In spite of a marked effect of Rubellin on the electrocardiogram, viz., a depression of the S-T segment and a prolonged P-R interval, there was no nausea or vomiting or any other symptoms usually associated with digitalis administration. The patient did not complain throughout the treatment, and as his condition improved he was later discharged.

CASE 8

Mr. A.C. 63, male, was admitted into hospital 13 May 1946 with congestive cardiac failure. He had been in hospital three years previously suffering from coronary thrombosis, and since his discharge he had been continuously short of breath. This had become progressively worse until he was dyspnoeic even when resting. There had been oedema of the feet at intervals during the last three years. This would disappear after a night's rest, but lately, even rest made no difference. The cervical veins were distended, there was oedema of the feet and ankles. There was dullness over both lung bases and numerous coarse crepitations were heard. The liver was two fingerbreadths below the costal margin and tender. The retinal arteries appeared to be sclerotic.

At the commencement of treatment the electrocardiogram showed that the patient had auricular fibrillation with a heart rate of 167 beats per minute. The venous pressure and the circulation time could not be estimated as the veins were not suitable. In spite of two days' rest in bed the heart rate was increasing. Treatment was begun on the morning of the 15th with an injection of 0.21 mg. Rubellin. Within ten minutes the heart rate decreased to 150 beats per minute. That same evening the heart rate was 125. He was then given a second injection and within 20 minutes the heart rate was 110 (Fig. 124). The cervical veins were no longer distended and he was reclining more comfortably



CASE 8 (A.C.). Dose 0.21 mg. Rubellin (three injections).

Fig. 120. Before treatment. Rate 167 beats per minute. T_1 inverted, T_3 and T_4 upright.

Fig. 122. Two-and-a-quarter hours after injection (first). Heart rate 155 beats per minute.

Fig. 124. Twenty minutes after the second injection. Heart rate 110 beats per minute. T_1 shallower and T_4 inverted.

Fig. 126. Twenty minutes after the third injection. Heart rate 82 beats per minute. T_1 upright, T_3 inverted, T_4 more inverted.

Fig. 129. Five days after the third injection. T_1 almost iso-electric, T_2 and T_3 upright, T_4 no more inverted.

in bed. A third and final injection was given on the following day. Within 20 minutes, i.e., 26½ hours after commencement of treatment, the heart rate was 82 (Fig. 126). The liver was one fingerbreadth below the costal margin and the oedema had disappeared.

An interesting feature of the electrocardiograms was that the T waves which were upright before treatment became inverted, and those which were inverted became upright. As the effects of the Rubellin wore off, the T waves reverted to their original position. T_1 and T_4 were the first to change. T_1 which was originally inverted became iso-electric (Fig. 123). T_4 which was upright, commenced to invert. This was more noticeable in Figs. 124, 125, 126.

On 21 May, five days after the third injection, when the effect of the Rubellin was wearing off, Fig. 129 shows how the T waves were commencing to revert to their original position, which was finally shown on 3 June, 18 days after the third injection (Fig. 130).

The action of the Rubellin here resembled that of digitalis, as was shown by the decrease of the heart rate and the changes in the T waves. The patient had no ill effects from the injections. He made good progress and was subsequently discharged.

SUMMARY

1. The results of a series of experiments on the effects of Rubellin, a new cardiac glycoside of South African origin, on cats and human subjects are described.

As far as is known, this is the first and only report on the clinical use of Rubellin in man.

2. The dose of Rubellin for human use was established. The drug can be measured gravimetrically and need not be assayed biologically.

3. Experiments on cats confirmed the previous work that Rubellin has a digitalis-like action.

Electrocardiograms were recorded before and after the administration of the drug.

Toxic doses of the drug produced impure auricular flutter, ventricular paroxysmal tachycardia and widening of the QRS complex, while amounts considered as therapeutic produced a decrease of the cardiac rate without significant changes in the configuration of the complexes.

4. A total of 43 intravenous injections was given to fourteen patients, most of whom were in severe congestive cardiac failure.

One death occurred 21 hours after a single injection of 0.21 mg. This case had aortic disease and was in a moribund condition on admission to hospital.

5. Of the fourteen patients, eight suffered from hypertensive cardiac disease. Case 7 had bronchial asthma superadded; two suffered from cardio-vascular syphilis; one from rheumatic heart disease; one from myocardial disease following coronary thrombosis; one from arteriosclerosis and one from bronchial carcinoma with metastatic deposits in the heart.

Eight of the fourteen cases had normal sinus rhythm, four had auricular fibrillation and two auricular flutter.

Twelve of the cases were in congestive cardiac failure.

6. Rubellin was found to be efficient in both normal and abnormal rhythm, acting with best results in auricular fibrillation and congestive cardiac failure. Intravenously it alleviated all urgent symptoms within a very short space of time, thus greatly reducing the period of suffering.

It has been shown that the persistence of effect could last up to 19 days.

7. Rubellin reduced the heart rate in twelve cases.

8. While rubellin, in its speed of action, was found to approach strophanthin and digoxin intravenously, in its effect on the electrocardiogram, however, it resembled digitalis.

The *P* wave was markedly reduced in height in one case.

The *P-R* interval was prolonged in three cases.

QRS. No appreciable changes were noted in these complexes.

S-T segments were depressed in eight cases. There was inversion of the T wave where T was originally upright, and restoration to the upright where T was originally inverted in one case.

Extrasystoles were noted in three cases in which bigeminal rhythm was present.

The Wenckebach phenomenon was produced in two patients.

Auricular fibrillation was produced in one patient.

In two cases of auricular flutter, while the ventricular rate was decreased in both, the rhythm changed from regular to an irregular block in one of them.

9. There was a decrease in venous pressure in six cases of congestive failure.

There was a decrease in the circulation time in five instances in four cases and an increase in one case.

10. Loss of weight took place in five cases of congestive cardiac failure.

11. Reduction in size of the heart was noted radiologically in one patient.

12. The toxic effects of Rubellin were not greater than those of digitalis.

13. Experience suggested that in cases of severe advanced congestive cardiac failure, a single dose of Rubellin administered intravenously is capable of producing full action within 2 hours.

Digitalis by mouth could be given simultaneously. Rubellin has a quick action which lasts until the oral digitalis begins to take effect.

Rubellin would appear to be of value in cases of vomiting and unconsciousness and where immediate treatment of congestive cardiac failure is imperative, provided it is certain that no other digitalis body has been taken within the preceding 10 days.

14. At this early stage, comparison of Rubellin with strophanthin or digoxin for use intravenously in cardiac emergencies is not attempted. It is realized that there are other preparations of digitalis and digitalis bodies on the market suitable for intravenous use. Further clinical study is necessary before venturing an opinion on the possible clinical usefulness of Rubellin.

I am greatly indebted to Dr. Norman Sapeika for supplying me with Rubellin and for the facilities he gave me in his department for conducting the experiments on the cats.

I wish to thank Prof. J. F. Brock and Dr. Helen Brown for their

interest and kind permission in allowing me to treat the above cases.

I also wish to thank Mr. Buxton, Senior Pharmacist at the Groote Schuur Hospital for arranging with Saphar Laboratories for the weighing and putting the Rubellin into ampoule form convenient for use.

REFERENCES

Chavez, I. (1943): Arch. Int. Med., **72,** 168.
Fishberg, A. M. (1940): *Heart Failure.* London: Henry Kimpton, Ltd.
Isaacson, B. (1949): Thesis (M.D. University of Edinburgh).
Parkinson, J. (1936): Lancet, **1,** 1337, 1391.
Pick, E. P. (1940): J. Mt. Sinai Hosp., **7,** 181.
Russek, H. and Zohman, B. (1945): Amer. Heart J., **30,** 50.
Sapeika, N. (1944): S. Afr. J. Med. Sci., **9,** 31.
Sapeika, N. (1950): S. Afr. Med. J. (This *Journal*, p. 912).
Smith, A. L. (1942): Med. Times, February.
Watt, J. M. and Breyer-Brandwyk, M. (1942): *Medicinal and Poisonous Plants of South Africa.* Edinburgh: E. & S. Livingstone.
White, P. (1944): *Heart Disease*, 3rd ed. London: Macmillan & Co.

THE ACTIONS OF RUBELLIN

A GLYCOSIDE FROM *URGINEA RUBELLA* BAKER

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The active principles in the Urginea group of plants, of which more than 25 species have been recorded in South Africa, have not been studied adequately and there is little information about them. Investigations have been concerned mainly with extracts of the plants. Some of the facts about the toxic Urginea plants occurring in Southern Africa are given by Watt and Breyer-Brandwijk (1932) and by Steyn (1934, 1949).

A new glycoside named rubellin was isolated by Dr. P. G. J. Louw (Onderstepoort, Pretoria) from *Urginea rubella* Baker. It is a stable, crystalline, soluble glycoside with a bitter taste. Its chemical properties have been described by Louw (1949). A preliminary investigation of its pharmacological properties was reported by Sapeika (1944, 1946) and in more detail recently (Sapeika, 1950). A clinical study of the drug administered intravenously has been made by Isaacson (1950). A summary of previous work and further studies on the pharmacological actions of this potent glycoside are given in the present article.

In experiments on animals no marked local or gastro-intestinal irritation was observed, but in man pain and discomfort occurred if any of the drug solution used (0.21 mg. in 10 ml.) was placed in the perivenous tissues.

Injections in the frog (*Xenopus laevis*) did not produce convulsions, but with adequate doses death occurred from systolic arrest of the ventricle. Using the 16-hour mortality method with ouabain (international anhydrous) as the standard of comparison, the potency of rubellin from determinations made on several occasions and in diffffferent seasons of the year, was found to be greater than that of ouabain. It is also more active than its derivative prorubellidin (a sugar-free glycoside obtained by Louw from acid hydrolysis of rubellin). The relative potency of certain glycosides is, in descending order: rubellin (121), ouabain (international anhydrous) (100), prorubellidin (50.5), strophanthin (44), lanatoside C (31), digoxin (19), digitoxin (3.6).

In the albino rat the subcutaneous injection of 0.001 mg. per gramme body weight caused death without signs of central nervous stimulation. By mouth 0.006 mg. per gramme body weight failed to cause death. In cats an intravenous dose of 0.1 mg. per kg. body weight caused death, whereas 1.0 mg. per kg. orally produced no disturbance.

On isolated frog hearts rubellin produced the typical 'digitalis' action with concentrations of 1 in 6 million; auriculo-ventricular block was sometimes observed. Electrocardiographic studies on the perfused isolated heart showed widening of the R wave, depression of ST and progressive shortening of this segment until the T wave was lost in the downward limb of R or became inverted. Perfusion with dibenamine hydrochloride 1:60,000 did not prevent the action of rubellin 1:300,000. Stimulation of the isolated ventricle with rhythmical electrical shocks showed that rubellin increased but then decreased the excitability of the myocardium. The coefficient of elasticity of the ventricle in contracture was increased.

In frogs anaesthetized with urethane, rubellin produced reduction in voltage, slowing, extrasystoles and finally disappearance of the lymph-cardiogram curves recorded from the posterior lymph hearts of *Xenopus laevis*. The lymph heart may beat long after the systemic heart (electrocardiographically recorded) has stopped, and it eventually ceases in diastole. Unlike certain other steroids rubellin does not produce ovulation in Xenopus.

Typical 'digitalis' effects were observed on the isolated mammalian (cat and rabbit) heart, and on the heart and blood pressure in the intact animal, e.g. after the intravenous injection of rubellin 0.1 mg. per kg. Electrocardiographic records showed slowing of the heart, prolongation of PR, widening of QRS, ectopic rhythm and tachycardia. Dibenamine hydrochloride 5 mg. per kg., injected five or 10 minutes before the administration of rubellin, failed to prevent the cardiac changes including ventricular fibrillation produced by the glycoside.

To elucidate a possible peripheral mode of action of rubellin in the cat studies were made with small doses on arterial and venous pressure, and intestinal and limb volume, but no significant change in the size of the vessels was observed; in the isolated hearts of cats, rabbits and guinea pigs, no significant change in coronary outflow was observed.

Rubellin does not increase the coagulability of normal whole human blood *in vitro* (Lee-White method). Urinary secretion was only slightly increased after intravenous injection of the drug in rabbits anaesthetized with urethane, and with fatal doses the output was diminished. The smooth muscle of the intestine and uterus of cat and guinea-pig was stimulated by rubellin 1:500,000; atropine failed to abolish the contraction of the intestine but adrenaline produced relaxation of the stimulated intestine and uterus.

SUMMARY

The actions of rubellin, a cardio-active glycoside from *Urginea rubella*, are described.

Thanks are due to Dr. P. G. J. Louw (Onderstepoort, Pretoria) for the supply of rubellin.

REFERENCES

1. Isaacson, B. (1950): This *Journal*, p. 901.
2. Louw, P. G. J. (1949): Nature, **163,** 30.
3. Louw, P. G. J. (1949): Onderstepoort J. Vet. Sci. Anim. Indust., **22,** 313.
4. Sapeika, N. (1944): S. Afr. J. Med. Sci., **9,** 31.
5. Sapeika, N. (1946): S. Afr. J. Med. Sci., **11,** 135.
6. Sapeika, N. (1950): Thesis, M.D. (University of Cape Town).
7. Steyn, D. G. (1934): *Toxicology of Plants in South Africa.* Johannesburg: Central News Agency.
8. Steyn, D. G. (1949): *Vergifting van Mens en Dier.* Pretoria: J. L. van Schaik.
9. Watt, J. M. and Breyer-Brandwijk, M. G. (1932): *The Medicinal and Poisonous Plants of Southern Africa.* Edinburgh: E. & S. Livingstone.

NEW PREPARATIONS AND APPLIANCES

ANTABUS

Antabus is the new medicinal treatment for alcoholism. By producing in the patient an association between alcohol and unpleasant physical reactions, it creates an aversion to alcohol.

This aversion renders the alcoholic more amenable to psychotherapy. For this reason, Antabus should only be administered under medical supervision and with the knowledge of the patient, in order that full advantage may be taken of the psychological reactions.

When a patient takes alcohol after having been given Antabus he experiences severe flushing, palpitations, dyspnoea, accelerated pulse rate and, particularly after large doses of alcohol, nausea and vomiting. This is followed by drowsiness, with complete recovery after sleep.

Antabus is only slightly toxic. A single dose of 2 grammes given by mouth to humans causes no symptoms, neither do daily doses of 0.25-0.75 gramme given daily for several months *except after intake of alcohol.*

Antabus produces an increased concentration of aldehyde in the blood by upsetting the normal combustion of alcohol. Absorption from the gastro-intestinal tract is slow, therefore Antabus must be given 3-4 hours before the intake of alcohol in order to obtain the maximum response.

As in the case of all new therapy, particular care should be exercised in patients with organic diseases, and especially with patients having cardiovascular diseases. Further, Antabus should be administered with extreme care to a patient in a state of intoxication. Because of violent reactions which may ensue, strict supervision should be maintained.

After a thorough physical, psyhiatric and social evaluation of the patient has been made, the procedure is as follows:—He is given two to three tablets of Antabus in one dose and two tablets the next day. He is warned that he will experience extreme physical discomfort if he partakes of alcohol, and is requested to consult his physician two or three days later. Then, under supervision he is encouraged to drink an accustomed amount so that he may experience the effect. Some patients have already experienced the effect after the intake of alcohol, as they have taken drink despite the warning.

After the effects have been experienced, a daily dose of half to one tablet is sufficient to maintain hypersensitivity to small amounts of alcohol.

Experience has shown that a patient relatively soon reaches a stage where he believes he is able to do without Antabus. However, with a view to possible recurrence, it is necessary to continue the treatment for a long time, until the patient is socially restored.

Readjustment and rehabilitation of the alcoholic is largely dependent on the tactful and co-operative attitude of the family, and it is important that patients and their relations should keep in touch with their physician, and that patients are encouraged to carry through the treatment. Measures should be taken to correct the underlying personality disorders and to adjust specific mental hazards.

THE BENEVOLENT FUND

The following contributions to the Benevolent Fund during August 1950 are gratefully acknowledged:

Votive Cards: *In Memory of*:

Mrs. T. J. Howell *by* The Ophthalmological Society of South Africa, Dr. L. Staz.
Miss Mary Jane Douglas *by* Dr. Margaret S. Brown.
Dr. J. de Ridder *by* Dr. B. P. Friedland.
Mr. Ernest Rouillard *by* Dr. G. Stafford Mayer.
Dr. W. R. Fyvie *by* Dr. R. B. Peckham, Dr. H. A. Kalley.
Mr. Molteno *by* Mr. L. B. Goldschmidt.
Dr. S. F. Silberbauer *by* Dr. and Mrs. J. S. du Toit, Dr. F. W. F. Purcell, Dr. and Mrs. F. O. Fehrsen, Dr. L. Blumberg, Dr. and Mrs. Lance Impey, Dr. A. J. Ballantine, Dr. F. Sutton Charnock, Mr. L. B. Goldschmidt, Dr. Vernon Brink, Dr. F. F. Petersen, Dr. and Mrs. Brian Porter, Dr. A. W. S. Sichel, Dr. H. A. Moffat, Dr. A. I. Goldberg, Dr. R. W. Claassens, Dr. and Mrs. D. P. Marais.
A. Campbell *by* Dr. C. E. L. Burman.
Dr. H. Pillemer *by* The Medical Staff of the Office of the Union Health Department.
Dr. D. F. Theron *by* Dr. C. F. Krige.
Mrs. F. C. Willmot *by* Dr. A. W. S. Sichel.

Total Amount Received from Votive Cards:	34	10	0

Services Rendered to:

Dr. W. R. Fyvie *by* Dr. C. A. V. Ovendale, Dr. N. M. L. Lund.

Total Amount Received from Services Rendered:	15	0	0

Donations:

Competition for the Campbell Cup (Cape Western Branch)	2	7	6
O.F.S. and Basutoland Branch of the S.A. Ex-service Medical Officers' Society	9	13	3
One of Dr. Watt's patients	5	5	0
Dr. G. M. Fox	2	0	0
Cape Western Branch Members	6	6	10
	£75	2	7

PASSING EVENTS

OPHTHALMOLOGICAL SOCIETY OF SOUTH AFRICA

This Society held its annual General Meeting at the Groote Schuur Hospital on Friday, 8 September at 8 p.m.

Dr. L. Staz of Johannesburg, the newly elected President, was the only visitor from elsewhere.

The following is the new Council of the Society:

President: Dr. L. Staz (Johannesburg); *Secretary and Treasurer*: Dr. J. Guilliaume Louw (Cape Town); *Vice-Presidents*: Dr. R. L. H. Townsend (Cape Town), Dr. J. K. de Kock (Cape Town); *Members of Council*: Dr. T. J. Howell (Johannesburg), Dr. Lucas Young (Pietermaritzburg), Dr. H. Kaye (Johannesburg).

Among the subjects discussed were the questionnaire from the S.A. Medical and Dental Council with regard to specialist training, and the provision of ophthalmological services in the country districts.

SOUTH AFRICAN COMMITTEE ON STUDY AND TRAINING IN THE UNITED STATES

Applications for scholarships and fellowships tenable at American universities and colleges during the academic year beginning in September 1951 are now being received by the South African Committee on Study and Training in the United States, which has its headquarters in Pretoria.

Full information and application forms may be obtained from the Public Affairs Officer, American Embassy, Pretoria. Applications must be filed by 1 November 1950.

Dr. M. H. de Kock, Chairman of the Committee, states that the Institute of International Education, New York, has asked the Committee to recommend 15 candidates for about five scholarships. Fields of study are not specified.

Applicants must have completed at least two years of study at the university level. They must be residents of the Union, must intend to return to South Africa after study in the U.S., and must be between the ages of 18 and 35 as of 1 September 1951.

Last year applications were restricted to graduate students. The South African Committee recommended ten applications to the Institute of International Education. Five offers of scholarships and fellowships resulted. Two were accepted, one is still pending, and two were declined for financial reasons.

CORTISONE

It is reported that limited amounts of Cortisone have been made available for distribution to 6,500 hospitals in the United States. Three vials, each containing 300 mg., will be allotted to each of the institutions for the purpose of investigating the treatment of rheumatic diseases.

* * * *

Prof. J. F. Brock left South Africa on 14 October on a period of secondment to the World Health Organization, to study the clinical features, aetiology and ecology of kwashiorkor (malignant malnutrition) throughout Central Africa. He will be back early in the new year.

* * * *

Dr. Eugenie Bosman, the eldest daughter of Mr. and Mrs. G. D. Bosman of Sunnyside, Pretoria, has announced her engagement to Dr. J. Coetzer, youngest son of Mr. and Mrs. E. Coetzer of Pretoria North.

* * * *

Congratulations to Dr. and Mrs. N. Sapeika of Cape Town on the birth of a son.

* * * *

Dr. M. P. van Huyssteen of Swellendam expects to leave for England at the beginning of next year. He will do post-graduate study in ophthalmology.

* * * *

Congratulations to Dr. and Mrs. Abe Levitt of Barkly West on the birth of a son on 8 October 1950.

* * * *

We regret to record the death of Dr. James McCord, founder of the McCord Zulu Hospital, at Oakham, Massachusetts, on 6 October 1950.

REVIEWS OF BOOKS

MEDICINE OF THE YEAR

Medicine of the Year, Second issue 1950. Editorial direction by John B. Youmans, M.D. (Pp. 184. 40s.) London: J. B. Lippincott Company.

Contents: 1. Internal Medicine. 2. Cardiovascular Diseases. 3. Respiratory Diseases. 4. Allergy. 5. Endocrinology and Metabolism. 6. Dermatology. 7. Neurology. 8. Psychiatry. 9. Obstetrics. 10. Gynecology. 11. Pediatrics. 12. General Surgery. 13. Fractures. 14. Orthopedics. 15. Otolaryngology. 16. Ophthalmology. 17. Anesthesiology. 18. Urology. 19. Neurosurgery. Index.

This is the second volume of *Medicine of the Year* edited by Dr. J. B. Youmans, and it presents in a critical form the significant advances and developments of the year 1949. A lot of ground is covered and, as can be seen from the table of contents, all the main specialities are dealt with by a team of writers from all over the United States. Unlike the series of the Year Books with which we are familiar, this volume deals with subjects in a discursive manner, and not paper by paper, and the references are tabulated at the end of each section; in other words, the book is a series of compact reviews of many subjects, well written, clear and, above all, critical. The several manufacturing firms of drugs send to all doctors free of charge similar brochures written in a similar strain. The forty shillings one will have to pay for this book under review is the price one has to pay for an independent and critical opinion so lacking in many of the aforementioned blurbs. It is impossible in a review of a book like this to be able to do any more than to recommend it to those who wish to be reasonably aware of recent advances in many subjects in as painless a way as possible.

THE HUMAN BREAST

The Breast: Structure : Function : Disease. Edited by F. D. Saner, M.B., B.Ch. (Camb.), F.R.C.S. (Eng.). (Pp. 316 + vi. With 192 illustrations, including colour plates. 45s.) Bristol: John Wright & Sons Limited. London: Simpkin Marshall Limited.

Contents: 1. The Structure of the Breast. 2. The Function of the Breast. 3. Abnormalities of Structure and Function. 4. Examination and Diagnosis. 5. Mammary Dysplasia: Chronic Mastitis. 6. Benign Tumours, Chronic Infective Lesions. 7. The Nipple and Skin. 8. Cancer: General Considerations. 9. Cancer: Invasion of the Internal Mammary Lymphatic Chain. 10. Cancer: Treatment. 11. Radiotherapy. 12. The Plastic Contribution to Breast Surgery. Appendix. Statistical Data on Breast Cancer. Index.

This book is edited by Saner and written by a number of authors. The structure of the breast is fully described. Of most particular value is a concise presentation of the features peculiar to particular ages and states of functional activity. It is well illustrated. The text is clear and gives an interesting short description of lymphatic pathways that may be opened up under abnormal conditions. A simple routine of hygiene for the management of the breast and nipple during pregnancy and lactation is outlined. The management of the failure of lactation is adequately treated.

Abnormalities of structure and function are then described. It might be held that this is a somewhat cursory survey of this aspect, but the whole book is obviously written more for the clinician than for the individual particularly interested in academic discussions. A very useful section entitled *Examination and Diagnosis* covers some 16 pages. The subject of mammary dysplasia is discussed along generally accepted lines. There is a useful outline of treatment for mastodynia.

The rest of the book virtually deals with tumours, innocent and malignant and, as is to be expected, mainly with malignant tumours. There is not very much new in the general account except for a very welcome description of the anatomy of the internal mammary lymphatic chain, which is illustrated by line drawings. The question of second intercostal space biopsy as a preliminary to mastectomy is discussed. Carcinoma of the breast and more particularly radiotherapy are reviewed at considerable length and here the general reader will find much information that will be new to him.

The book should serve a very useful function in the library of any general surgeon and would be of interest to the radiotherapist and the general practitioner as well.

NEUROLOGY AND NEUROSURGERY

Practical Neurological Diagnosis with Special Reference to the Problems of Neurosurgery. By R. Glen Spurling, M.D. (Pp. 268 + xx. With 101 illustrations. 37s. 6d. Fourth edition, 1950.) Illinois: Charles C. Thomas. England: Blackwell Scientific Publications, Limited.

Contents: 1. The Neurological Examination: History-Taking and General Considerations. 2. Cranial Nerves. 3. The Cerebrum. 4. The Cerebellum. 5. The Spinal Cord. 6. The Reflexes 7. The Cerebrospinal Fluid. 8. Roentgenologic Diagnosis. Appendix: 1. Outline of the Neurological Examination. 2. References. Index.

This book, an old friend of many people interested in neurology in its various phases, has now reached its fourth edition.

The sequence of the subject matter has been somewhat altered and certain parts have been completely rewritten. A section on the hypothalamus has been added.

The previous excellence of this book is well enough known, and scrutiny of the two new sections on the cerebellum and the hypothalamus show, once again, that the author strikes a happy note of simplifying things which at first appear to be difficult.

Clinical tests, as in the other editions, are adequately reviewed. The whole work seems to avoid contentious matters and remains now, as always, a very useful handbook for practical work; in fact, just what it sets out to be.

This book, like its predecessors, should find its place on the shelf of anyone interested in this particular subject and, in addition, it is an excellent manual for general practitioners and students.

VENEREAL DISEASES IN SOUTHERN RHODESIA

Report on A Venereal Diseases Survey of the African in Southern Rhodesia. By R. R. Willcox, M.B., presented to the Secretary for Health, October 1949. With 37 tables.

Contents: 1. Introduction. 2. Incidence of Venereal Disease as a Whole. 3. Gonorrhoea. 4. Soft Sore. 5. Lymphogranuloma Venereum. 6. Granuloma Inguinale. 7. Syphilis: Incidence. 8. Syphilis in the Adult Native. 9. Congenital Syphilis. 10. The Problems of Yaws and Endemic Syphilis. 11. Other Conditions Encountered in Venereal Diseases Clinics. 12. The Normal African. 13. The Venereal African. 14. Social Aspects of Venereal Disease Prevention.

Dr. Willcox's report describes a six months' tour of Southern Rhodesia in which he investigated the possibilities of increasing the speed and efficiency of treatment of the African with venereal disease.

Approximately 70,000 new cases of venereal disease (3.7% of the population) report for treatment each year; and venereal diseases account for 20% of all admissions to Government clinics and 30% of in-patient days in hospital.

The gonorrhoea-syphilis rate is the reverse of that in Europe, probably because all genital sores have been described as syphilis and gonorrhoea is considered by many sufferers too trivial to require attention. Urethral stricture is rare, an observation which confirms the belief of many conservative venereologists that the indiscriminate use of urethral instruments is more harmful than is gonorrhoea. Penicillin had a poor reputation as a cure for gonorrhoea in some quarters. The reason for this was that it had been used wrongly, or for cases of non-gonococcal urethritis, trichomonas vaginitis, etc., where it would have little or no effect. Penicillin, one injection of 300,000 units in a retarding vehicle, is recommended as the treatment of choice for gonorrhoea.

Chancroid is common and has hitherto been treated as syphilis. This waste could be avoided by proper diagnostic methods as chancroid reacts well to sulphonamides. Lymphogranuloma inguinale, another condition treated with antisyphilis remedies in the past, should be treated with sulphonamides and early aspiration of fluctuant buboes. Granuloma venereum is relatively rare and streptomycin treatment is advocated. The increased cost would be offset by the shorter stay in hospital.

The greatest defect of the old standard arsenic-bismuth treatment of syphilis is the very high default rate. Worthwhile results are only obtained if patients attend regularly over six months; and the percentage of patients of any race who do so is not very large. Dr. Willcox advocates, for early syphilis, the use of eight daily injections of 600,000 units Penicillin in a retarding medium, with, in addition, a 10-week course of bismuth for women. A trial of 'single shot' treatment with 2,400,000 units procaine penicillin is suggested. If this were proved reasonably successful it would be very useful for patients in remote areas.

It is naturally impossible to give treatment schedules for all the possible varieties of late syphilis but Dr. Willcox wisely recommends a preparatory course of iodides and bismuth before using penicillin or arsenicals, in order to minimize the chances of therapeutic shock or paradox. The reviewer has also recently had evidence suggesting that a cautious start is advisable in treating late syphilis in the African Native.

An important basic recommendation is that Penicillin be used in all pregnant women with clinical or serological evidence of syphilis. In the notes on congenital syphilis it is stated that Hutchinsonian teeth and interstitial keratitis were very rarely seen among the many children examined. This has not been the reviewer's experience in the Union.

There is also a description of 'njovera' which appears to be an extra-venereal variety of syphilis, usually contracted in childhood and analogous to bejel. Short notes are given on non-gonococcal urethritis, trichomonas vaginitis and other diseases of the genitals. Dr. Willcox suggests giving a week's home treatment with stovarsol pessaries, as well as Penicillin, to women with copious vaginal discharges. This would seem wasteful as this amount of treatment could cure only a very few cases.

A miniature 'Kinsey report' describes the sexual habits of the venereal and the non-venereal African. The prostitute is a very common source of disease. The organized 'Tea Party' is apparently a very important factor in the spread of disease in Rhodesian towns.

The idea that licensed brothels could be an answer to the problem is rightly dismissed; but if the present conditions in industry have to continue it is suggested that women in compounds be registered and given prophylactic penicillin and bismuth.

Dr. Willcox points out, once again, that loss of tribal discipline is not being replaced by anything of importance; and he suggests that the only possible compensation is provision for the establishment of a home in which the worker can live a dignified existence and raise a family. The other suggestions for propaganda, good recreational facilities (not to be allowed to degenerate into brothels), etc., show that the problem in Rhodesia is very much the same as that presented by any army in war time. This report might well have had for its sub-title 'Diagnosis Precedes Treatment', the motto of the late Mr. Russell Howard. The only possibility of reducing endemic venereal diseases among African Natives seems to lie in proper diagnosis and treatments sufficiently rapid to give a higher percentage of cures before the average patient inevitably defaults.

Dr. Willcox's recommendations from the medical angle are sound and simple and are bound to produce good results when they can be applied. His sociological suggestions, without which complete success will never be attained, are likely to be longer delayed.

ASTHMA

Asthma. By Clement Francis, M.A., M.C., B.Ch. (Pp. 49 with 3 figures and 2 colour plates. 5s.) London: William Heinemann Medical Books Ltd. 1950.

Contents: 1. Aetiology and Pathology. 2. Cauterisation of the Nasal Septum. 3. Skin Testing and Desensitisation. 4. Nose and Throat Operations. 5. Anaesthesia. 6. Medicinal Remedies. 7. Aspirin Sensitivity. 8. Physical and Breathing Exercises. Index.

This booklet gives a fairly comprehensive and up-to-date survey on a difficult medical problem by someone who has devoted a considerable amount of time to its study.

Besides the usually accepted forms of treatment, the writer advocates the delicate application of a fine cautery point to the mucous membrane of the nasal septum as the most effective therapeutic measure. The improvement that usually results from such treatment is said to be due to an action on the nerve endings in the septal mucosa and thence reflexly on the sympathetic system as a whole.

Dr. Francis warns his readers about the effects of sinus surgery on asthmatics, but states that properly planned sinus operations will usually benefit these patients if the patient is not aspirin sensitive—a condition found in approximately 5% of asthmatics.

The many practical points found in this volume should prove a useful guide to medical practitioners in their handling of these cases.

TROPICAL DERMATOLOGY

Dermatologie der Tropen. Onder Redactie van Dr. R. D. G. Ph. Simons. (Bl. 620. F.35.) Amsterdam: Scheltema en Holkema's Boekhandel en Uitgeversmaatschappij N.V.

Although tropical dermatology is well documented in the journals, the reviewer cannot recall any adequate modern textbook devoted to the subject. Dr. Simons and his collaborators must be congratulated on producing a most useful addition to medical literature.

A major part of the book is contributed by Dr. Simons, whose experience has been mainly in the Netherlands East Indies. Chapters on diseases in other areas have been written by authorities on these regions; and among the contributors are Aldo Castellani, Pardo Castello and Howard Fox, to mention only a few.

The introductory chapter by Dr. Simons deserves special mention. In this he gives a short historical note, a survey of what he rightly calls the terminological jungle of tropical dermatology, and an account of the common skin diseases as seen in, and as modified by the tropics. Other chapters of general scope cover children's diseases and tropical dermatology for the ship's surgeon.

The chapters on specific diseases or groups are all notable for clarity and good, up-to-date documentation. The numerous photographs are, with one glaring exception (Fig. 346), clear and well chosen. There are no important omissions in the field covered and overlapping by the various contributors has largely been avoided.

There is, reasonably enough in a book of this scope, no particular chapter on syphilis, but it receives many mentions and illustrations in regard to differential diagnosis. Lymphogranuloma inguinale and granuloma venereum are fully described.

The newer antibiotics are mentioned in the appropriate settings, but as is usual at the present time, there have been advances since the book went to press. On the whole, however, the information on the newer remedies is remarkably complete.

The book is well bound, printed on good paper and the index is informative and accurate.

YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY

The 1949 Year Book of Dermatology and Syphilology (November 1948-December 1949). Edited by Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. (Pp. 514. With 76 illustrations. $5.00.) Chicago: Year Book Publishers, Incorporated.

Contents: Acne Vulgaris and Its Management. 1. Treatment and Prevention (Exclusive of Venereal Diseases). 2. X-ray and Other Physical Therapy. 3. Eczematous Dermatitis and Urticaria (Allergic and Nonallergic); Allergy. 4. Drug Eruptions (Allergic and Nonallergic). 5. Miscellaneous Hematogenous Dermatoses. 6. Other Dermatoses. 7. Cancers; Precanceroses; Other Tumours. 8. Mycosis Fungoides; Leukemia. 9. Fungous Infections. 10. Other Infections; Infestations. 11. Venereal Diseases (Exclusive of Gonorrhea). 12. Investigative Studies. 13. Miscellaneous.

The 1949 *Year Book of Dermatology and Syphilology* maintains the high standard of previous editions. The editors survey the literature of the world and no work of any importance pertaining to the speciality appears to have been overlooked.

It is claimed that the year 1949 may have excelled its immediate predecessors in both quantity and quality of progress made in dermatology. Thus, in the line of therapy, ACTH, cortisone, procaine-penicillin, aureomycin, chloromycetin, streptomycin and vitamin D_2 proved their value in 1949. Much progress was also made in diagnosis and investigation of the physiological, histochemical and biological aspects of the skin's components in health and disease.

The abstracts, as can be seen by the titles of the chapters, cover practically the whole field of the speciality. The brief criticisms at the end of each abstract are masterpieces of erudition combined with brevity.

The first chapter of each *Year Book* is usually devoted to some common dermatoses. This year the editors devote the first 30 pages to acne vulgaris. No practitioner, specialist or otherwise, can afford to miss studying this informative work.

YEAR BOOK OF ENDOCRINOLOGY

The 1949 Year Book of Endocrinology, Metabolism and Nutrition (December 1948-January 1949). Endocrinology edited by Willard O. Thompson, M.D. Metabolism and Nutrition edited by Tom D. Spies, M.D. (Pp. 550. $4.75. With 101 illustrations.) Chicago: The Year Book Publishers Incorporated.

Contents: *Endocrinology:* Introduction. 1. The Pituitary. 2. The Thyroid. 3. The Parathyroids. 4. The Adrenals. 5. The Testes. 6. The Ovaries. 7. Miscellaneous.
Metabolism and Nutrition: Introduction. 1. Pancreas and Liver. 2. Alimentary Tract. 3. Hemopoietic System. 4. Cardiovascular System. 5. The Brain and Nervous System. 6. Genitourinary System. 7. Dermal and Skeletal Systems. 8. Malnutrition and Undernutrition. 9. Therapy.

The *Year Book Series* of abstracts from the world's medical literature is well known, and this particular volume on *Endocrinology, Metabolism and Nutrition* is well up to the high standard one has come to expect; 1949 was the year in which ACTH and Cortisone were shown to have such a tremendous effect on rheumatoid arthritis and on other diseases. The early work, almost all performed in the United States, is well discussed and presented. More recent work has emphasized that the caution originally noted by the first workers should be maintained until much more is known about these amazing hormones.

Radioactive iodine in the treatment of Graves' disease has not been generally used in South Africa, so it is interesting to note that the consensus of opinion so far is that its ultimate status has not yet been determined. It is mostly agreed that its use is indicated in patients who are poor surgical risks and in those in whom the disease persists or recurs. No serious complications in its use have been reported and it appears to be a safe form of treatment.

The determination of foetal sex based on the work of Nieburgs, a former colleague of the reviewer, has been discussed. The technique is based on changes in the vaginal cells, and the greatest percentage of specific smears is found between the 18th and 26th weeks of pregnancy. In the number of cases investigated so far the sex was accurately predicted in 86%. The reviewer very vividly remembers the mounting excitement in the labour wards with the researcher's anxious face at the level of the perineum to note the sex of the infant. The cries of joy of a successful prediction, the squalling of the infant and the clash of pots and pans all made an otherwise prosaic affair exciting and invigorating. The method is not yet, however, much better than an inspired guess, and much more work must be done.

The volume is full of interesting and informative data, and is worth having for those who wish to keep abreast of a fast-growing subject.

THE MARCH OF MEDICINE

The Future in Medicine. The March of Medicine, 1949. Number XIV of The New York Academy of Medicine Lectures to the Laity. (Pp. 160. $2.50.) New York: Columbia University Press. 1950.

Contents: 1. Foreword. 2. Introduction. 3. Law and Medicine. 4. The Endocrines: Servants or Masters? 5. Science under Dictatorship. 6. Blood and Man. 7. The Criminal within Us. Index.

This little volume is intended primarily as a contribution to the laity. The articles, however, are so carefully considered and presented that they form what is really a most adequate survey which will interest the medical practitioner as well as the layman. The volume is the fourteenth in a series entitled *The Future in Medicine* and is a most excellent synopsis of every field tackled.